USAID
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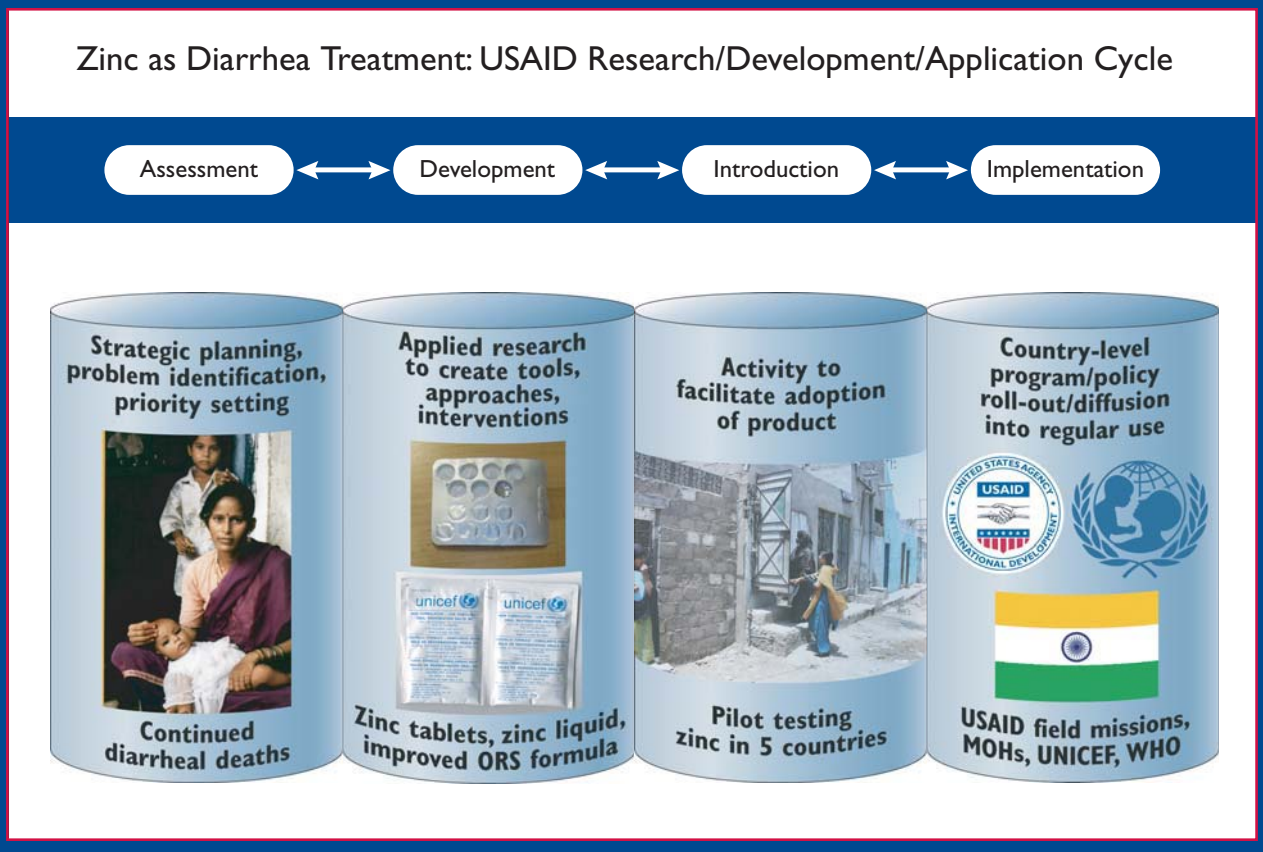
Report to Congress

Health-Related Research and Development Activities at USAID



June | 2005

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Acronyms and Abbreviations

ACT	Artemisinin-based combination therapy
AD	Auto-disable
AMR	Antimicrobial resistance
ANC	Antenatal care
BD	Becton, Dickinson and Company
CA	Cooperating agency
CDC	Centers for Disease Control and Prevention
CIDA	Canadian International Development Agency
CMM	Care management map
CS/MH	Child survival/maternal health
DAIDS	Division of AIDS
DOD	Department of Defense
DOTS	Directly observed treatment, short course
EPI	Expanded Program on Immunization
FDA	Food and Drug Administration
FMVCC	Federal Malaria Vaccine Coordinating Committee
FP/RH	Family planning/reproductive health
FY	Fiscal year
GAVI	Global Alliance for Vaccines and Immunization
GHAVE	Global HIV/AIDS Vaccine Enterprise
GSK	GlaxoSmithKline
HHS	Department of Health and Human Services
IAVI	International AIDS Vaccine Initiative
ICDDR,B	International Centre for Diarrhoeal Disease Research, Bangladesh
ID	Infectious diseases
ITN	Insecticide-treated mosquito net

IUD	Intrauterine device
IVACG	International Vitamin A Consultative Group
MDR-TB	Multidrug-resistant tuberculosis
MMV	Medicines for Malaria Venture
MOH	Ministry of health
MVDP	Malaria Vaccine Development Program
MVI	Malaria Vaccine Initiative
NGO	Nongovernmental organization
NIAID	National Institute of Allergy and Infectious Diseases
NID	National immunization day
NIH	National Institutes of Health
NMRC	Naval Medical Research Center
ORS	Oral rehydration salts
ORT	Oral rehydration therapy
PATH	Program for Appropriate Technology in Health
PAVE	Partnership for AIDS Vaccine Evaluation
PEPFAR	President's Emergency Plan for AIDS Relief
PVO	Private voluntary organization
RAPID	Rotavirus Vaccine Action Partnership for Introduction and Development
STI	Sexually transmitted infection
TBA	Traditional birth attendant
TDR	Special Program for Research and Training in Tropical Diseases
UNICEF	United Nations Children's Fund
USAID	U.S. Agency for International Development
VA	Vitamin A
VCT	Voluntary counseling and testing
VVM	Vaccine vial monitor
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

Executive Summary

Congress requested that the U.S. Agency for International Development (USAID) provide a report describing its role in the research, development, and application cycle and its efforts to coordinate research and development activities with other agencies. This report responds to this request and provides details on the amounts spent on research by health issue or disease, recipient, and stage of research or development funded.

From 2002 to 2004, USAID invested between 6 and 7 percent of its total health-related budget in research and development. In 2004, this percentage represented $155 million. That year, the largest amount of research funds was spent on HIV/AIDS related research, followed in descending order by research on family planning and reproductive health, research on infectious diseases, and research on child survival and maternal health, including polio and micronutrients.

The results of USAID-supported research have had significant public health impacts, starting with Oral Rehydration Salts (ORS), now used in about 85% of child diarrhea cases in almost half the world's children under 5. The results of vitamin A research now save approximately 1 million pre-school aged children a year. And, the impact of zinc, another USAID research product, on decreasing child mortality could be as or more significant than Vitamin A. By 2004, 2.5 billion autodisable syringes and 900 million vaccine vial monitors, both results of USAID-supported research, had been sold or distributed worldwide. USAID-funded research has resulted in food fortification programs, making fortified sugar, cooking oil and flours available to the majorities of the population of many countries. More recently, USAID research on natural family planning has resulted in the development of two new methods, both of which have shown to be very effective when used correctly. USAID supported large-scale efficacy trials of insecticide treated nets across Africa, which provided definitive data on the highly effective impact of ITNs for preventing malaria among the most vulnerable populations of women and children. This report further details the impact of research in many other areas.

USAID invests in research to identify and assess key health problems affecting populations in developing countries and to develop and introduce new vaccines, tools, and approaches to help resolve these problems. The objective of almost half of USAID research activities is to find ways to "introduce" and make life-saving interventions accessible to those most in need -- children under 5, mothers, people living with or at risk of HIV/AIDS and TB, and women and men of reproductive age. The other objectives of USAID research activities are to identify or assess major public health problems and develop a new tool or approach to help resolve these problems.

Other partners complement the different roles that USAID plays in the cycle from research to implementation. In some cases, for example, research to develop a malaria vaccine, the objective of U.S. Government partners is different from that of USAID - a short term vaccine to protect troops versus a long term vaccine to protect vulnerable women and children. In the case of Oral Rehydration Salts and Vitamin A, USAID's role began with the identification of the problem and the development of the intervention, right up to wide scale introduction, working with WHO and UNICEF. USAID's research role in yet other cases is to provide information necessary to the private sector to carry out large scale commercialization of new products such as fortified foods and long-lasting insecticide treated bed nets.

USAID's role in the development of microbicides, for example, is to focus research and development on safe, effective and acceptable microbicides to prevent HIV infection that have the appropriate cost and product characteristics for use in developing countries and, in some cases, offer dual-protection as a family planning method. USAID collaborates with NIH, CDC, and FDA to develop the U.S. Government's Strategic Plan for Microbicides.

This report details research that USAID has supported and its results. In some of the newer areas of research the report also looks at ongoing studies. One example of these is a soon-to-be commissioned review by Brian Sharp, Medical Research Council, Durban, South Africa, and Christian Lengeler, Swiss Tropical Institute, Basel, Switzerland to compare indoor residual spraying (IRS) and insecticide treated nets (ITNs) across a range of

malaria transmission settings in sub-Saharan Africa in terms of cost-effectiveness, impact on health measures, and operational constraints. The report, expected in early 2006, should provide clear, evidence-based guidance to National Malaria Control Programs and USAID missions on key factors to consider when selecting vector control interventions to ensure maximum public health effectiveness for money spent. Another example is the ongoing research on simple low-cost community care packages (warming, delayed bathing) that could reduce neonatal deaths by an average of 40 percent in low resource settings.

Section I

The six research areas included in Section I account for the majority of USAID health-related research and results over the past two decades. Section I describes each area and explains how it was identified. It also describes the role of USAID, its coordination with U.S. government agencies and other partners, and the main results of the research investment to date.

The six research areas are:

1) Vaccine development

2) Maternal, newborn, and child health interventions

3) Microbicides

4) Contraceptive technologies

5) Malaria

6) Tuberculosis

I. VACCINE DEVELOPMENT

Malaria Vaccine: USAID's research role is to speed the development of malaria vaccines to protect children and pregnant women from death and serious disease in malaria-endemic areas. USAID has had a critical catalytic role in moving the current set of vaccine candidates through the research process to field trials. As a result of USAID's investments over the years, two vaccine candidates are currently undergoing safety or efficacy trials in the field. USAID works with DOD partners such as the Walter Reed Army Institute of Research and the Naval Medical Research Center; HHS partners such as the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration; and the Malaria Vaccine Initiative, a Bill & Melinda Gates Foundation funded program.

HIV/AIDS Vaccine: USAID's research role accelerates the development and introduction of new vaccine candidates and technologies and helps link vaccine designers with manufacturers and developing-country sites suitable for testing promising HIV vaccine candidates. USAID supports HIV vaccine research as well as policy analysis and other work to pave the way for introducing vaccines when they become available. USAID works with the International AIDS Vaccine Initiative and the Partnership for AIDS Vaccine Evaluation (the U.S. government HIV vaccine coordination group) and would like to be involved with the Global HIV/AIDS Vaccine Enterprise as it unfolds.

Childhood Vaccines – Rotavirus and Pneumococcal Conjugate Vaccines: USAID's research role is to catalyze and coordinate clinical trials of refined rotavirus vaccine and a large-scale clinical trial of pneumococcal conjugate vaccine. USAID works with the World Health Organization (WHO), NIH, CDC, the British Medical Research Council, the London School of Hygiene and Tropical Medicine, the Program for Appropriate Technology in Health (PATH), and vaccine manufacturers. USAID's participation and investment in the Global Alliance for Vaccines and Immunization (GAVI) supported the selection of these two vaccines for a new approach to accelerated vaccine development and introduction in developing countries.

Vaccine- and Injection-Related Technologies: USAID anticipated the need for technologies that could prevent syringe and needle reuse and supported the development and introduction of the devices now known as auto-disable (AD) syringes and vaccine vial monitors (VVMs) to ensure that only potent vaccine is used. USAID works with WHO; the United Nations Children's Fund (UNICEF); PATH; Becton, Dickinson and Company; Pfizer Inc.; and GAVI. To date, 2.5 billion AD syringes and 904 million VVMs have been sold or distributed worldwide.

2. MATERNAL, NEWBORN, AND CHILD HEALTH INTERVENTIONS

Maternal and Neonatal Health: Since the launch of the Safe Motherhood Initiative in 1987, USAID has supported the development and testing of new technologies and community and facility approaches as well as meta-analyses to improve and transform maternal and neonatal interventions. USAID coordinates with WHO; host governments; U.S. and developing-country researchers NGOs/PVOs and universities in Nepal, Bangladesh, Egypt, Tanzania, Thailand, Pakistans, India, Peru, and Malawi; the World Bank, and the American College of Nurse Midwives. Some USAID-supported technologies and approaches – the home-based maternal record, for example – now are used in countries around the world, while others are still in the development and introduction stages.

Oral Rehydration Salts, Oral Rehydration Therapy: USAID supported research to develop and introduce oral rehydration salts (ORS) and oral rehydration therapy (ORT) to treat dehydration caused by diarrhea, especially the early development research undertaken by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). With support from USAID and other donors, ORS became the cornerstone of the WHO/UNICEF Program on Control of Diarrheal Diseases. In 33 countries containing almost half the world's children under age 5, use of ORS/ORT increased from about 33 percent of cases in 1990 to 85 percent by mid-decade. USAID recently supported WHO and other research partners in refining the ORS formulation. The new formulation, called reduced-osmolarity ORS, further reduces the need for intravenous therapy and is safe for treating both children and adults. UNICEF and WHO have adopted the new formulation as the global standard.

Micronutrients – Zinc: USAID-supported research built the evidence base that led to WHO and UNICEF signing a 2004 agreement revising the protocol for using zinc supplements to treat diarrhea. USAID is supporting work to introduce zinc into programs and is working with host governments to accelerate the adoption of the new recommendations for diarrhea treatment. USAID also supports product supply, guideline development, program planning, and marketing. USAID has supported the development of zinc formulations by manufacturers in a way that ensures thermostability in hot weather environments and under poor storage conditions. USAID works with WHO; the Johns Hopkins University Bloomberg School of Public Health, ICDDR,B, local universities, and international NGOs.

Micronutrients – Vitamin A: USAID supported the research that established the base of evidence for the discovery that two cents worth of vitamin A given to children every six months could reduce child mortality by 34 percent and fatality from measles by more than 50 percent, as well as reduce the severity of diarrhea and malaria. USAID continues to support research on the effects of vitamin A on maternal health and pregnancy risk. UNICEF, with procurement largely funded by the Canadian International Development Agency, now delivers 600 million to 800 million vitamin A supplements each year, saving the lives of approximately 1 million preschool children every year. More than 60 countries around the world have implemented vitamin A supplementation.

Food Fortification: USAID supported assessment research on vitamin A deficiency and anemia prevalence and the development and introduction research necessary for large-scale food fortification programs. This research has included stability and acceptability tests, technology trials, and stability trials, and has resulted in food fortification programs that have made fortified sugar, cooking oils, and/or flours available to the majority of the populations of Bangladesh, Nicaragua, Philippines, Zambia, Uganda, Eritrea, Morocco, West Bank/Gaza, and Ghana. USAID works with health, industry, and food ministries; bureaus of standards; the World Food Program; national associations of food producers, millers, growers, etc.; UNICEF, the Pan American Health Organization; the Micronutrient Initiative; and local universities.

3. MICROBICIDES

USAID supports research for the development of safe, effective, and acceptable microbicides that have the appropriate cost and product characteristics for use by women in developing countries to prevent HIV infection. This research program is coordinated through collaborations with other U.S. government agencies,

including NIH, CDC, and FDA, as well as other bilateral and multilateral donors, and both national and international organizations that are supporting or conducting activities related to microbicide research and development. These collaborations maximize efficiency and progress through the coordination of scientific plans, joint priority setting, sharing of resources, and learning through new data and experience. About three-quarters of USAID funding supports essential phase III clinical studies that are currently underway. The remaining quarter supports developing capacity at sites for future clinical studies, research on selected second-generation microbicide candidates, and product introduction issues.

4. CONTRACEPTIVE TECHNOLOGIES

USAID supports development research to improve existing and develop new contraceptive technologies and to identify and test innovative approaches to improving the effectiveness and efficiency of family planning (and related reproductive health) service delivery. USAID also supports introduction research to expand the variety of effective contraceptive methods available in USAID-supported family planning programs worldwide. USAID works with the Eastern Virginia Medical School; Family Health International; the Population Council; Georgetown University; PATH; WHO, CDC; NIH, FDA; the United Nations Population Fund; the U.K. Department for International Development; the Bill & Melinda Gates Foundation; the Hewlett Packard, Rockefeller, and Buffet foundations; Pfizer Inc.; Wyeth; Ortho-McNeil Pharmaceutical; Schering AG; and Organon. USAID-supported research has resulted in the availability of a wider variety of new contraceptives and improvements in the understanding of existing technology.

5. MALARIA

In addition to malaria vaccine development, USAID supports research to assess the feasibility, acceptability, safety, and impact of malaria prevention and treatment technologies and to monitor the spread of drug-resistant malaria. USAID also supports research to develop new drugs for treating both uncomplicated and severe malaria and new technologies for improved home management of malaria. In the 1990s, USAID supported early clinical trials of artemisinin-based combination therapy (ACT) in children in Africa. ACT is now the WHO-recommended treatment for malaria and is being rolled out throughout Africa. USAID is now funding operations research to evaluate the introduction of new ACT treatments in sub-Saharan Africa. USAID also supported groundbreaking trials of insecticide-treated mosquito nets (ITNs) that demonstrated they can reduce under-5 mortality from all causes by about 20 percent and reduce clinical cases of malaria by 40 percent to 50 percent. ITNs are now being scaled up and used throughout Africa. Malaria research is carried out through a variety of organizations, including WHO, CDC, the Medicines for Malaria Venture, the Kenan Institute of Asia, and U.S. Pharmacopeia.

6. TUBERCULOSIS

USAID supports research in areas critical for accelerating the introduction and global expansion of the DOTS (directly observed treatment, short course) strategy and improving DOTS program performance. USAID focuses on the development, evaluation, and introduction of new diagnostics, drug regimens, and approaches that will improve the DOTS strategy and are appropriate for use in low-resource countries, including effective approaches to TB-HIV co-infection. USAID's early support of the "ProTest" approaches to TB-HIV co-infection resulted in workable models for addressing co-infection that are now being scaled up in multiple countries in Africa and are also included in the WHO and Stop TB Partnership guidance on TB-HIV. USAID also supported clinical trials on TB drug regimens of the International Union Against Tuberculosis and Lung Disease (the Union). The study's results, published in October 2004, confirmed that a six-month course of treatment with a specific set of drugs was more effective than an alternate eight-month course with other drugs. These results are now included in the *International Standards of Care for TB Treatment*. USAID is currently supporting the development of new drugs in partnership with the Global Alliance for TB Drug Development. USAID's TB research partners include WHO; CDC; the Union; the TB Diagnostics Initiative at the Special Program for Research and Training in Tropical Diseases (a WHO/UNICEF/World Bank program); Johns Hopkins University; the University of Alabama, Birmingham; and the Global Alliance.

Section II

Fast Facts and Trends, 2002-2004

- USAID invests 6 to 7 percent of its total health-related budget in research and development. This percentage represented approximately $112 million in 2002, $123 million in 2003, and $155 million in 2004 (Table II.1).
- The proportion of funding obligated to research ranges from around 5 percent for child survival and maternal health (CS/MH)*, to between 5 and 10 percent for HIV/AIDS and family planning and reproductive health (FP/RH), to between 10 and 15 percent for infectious diseases (ID) (Table II.1).
- From 2002 to 2004, the total amount of funding for research grew from $112 million to $155 million. The health issue or disease with the largest single share of that funding for all three years was HIV/AIDS (37%, 37%, 46%), followed in descending order by Family Planning/Reproductive Health (29%, 32%, 24), Child Survival, Maternal Health, including Polio and Micronutrients (14%, 15%, 14%), Malaria (7%, 7%, 7%), TB (6%, 5%, 5%), and AMR, Surveillance and Other ID (7%, 4%, 3%). (Figures 11.3-11.5).
- While USAID/Washington centrally manages the largest number of research activities, the proportion of research managed by USAID missions increased from 15 percent of activities in 2002 to 21 percent in 2004 (Figure II.7).
- Introduction research is the largest share of research activities (45 percent); assessment and development research are at about the same level, around 27 to 28 percent (Figure II.8).
- USAID missions originate the majority of assessment research activities (60 percent missions, 40 percent USAID/Washington) (Figure II.8).
- USAID/Washington originates the majority of development research activities (75 percent USAID/Washington, 25 percent USAID missions) and introduction research activities (65 percent USAID/Washington, 35 percent USAID missions) (Figure II.8).
- The recipient of USAID's research investments include collaborating agencies and partners such as grantees and contractors; universities; NGOs/PVOs; host governments; the Centers for Disease Control and Prevention; the National Institutes of Health; and the Department of Defense (Table II.3).

* This percentage is lowered by the GAVI funds included in this overall account (between $55 and $65 million)

Amount/Percent of Health or Disease Area Funding Used for Research, FY 2002-2004

Health or Disease Area	2002		2003		2004	
	$ Mil	Percent of Total Funding	$ Mil	Percent of Total Funding	$ Mil	Percent of Total Funding
HIV/AIDS	$41	8%	$46	7%	$72	6%
Family Planning/Reproductive Health	$33	7%	$40	9%	$38	9%
Infectious Diseases (inclusive of AMR/other ID, malaria, TB)	$23	12%	$20	11%	$23	11%
Child Survival/Maternal Health (inclusive of polio and micronutrients)	$16	4%	$18	5%	$22	5%
Vulnerable Children	$0	0.06%	$ -	0%	$1	2%
Total Obligation on Research	**$112**	**7%**	**$123**	**6%**	**$155**	**7%**

Distribution of Total USAID Health-Related Research Funding by Each Major Health or Disease Area

Health or Disease Area	2002	2003	2004
HIV/AIDS	37%	37%	46%
Family Planning/Reproductive Health	29%	32%	24%
Infectious Diseases (inclusive of AMR/other ID, malaria, TB)	20%	16%	15%
Child Survival/Maternal Health (inclusive of polio and micronutrients)	14%	15%	14%
Vulnerable Children	0.02%	0%	0%
Total	**100%**	**100%**	**100%**

Section I

Introduction

Congress requested that the U.S. Agency for International Development (USAID) provide a report describing its role in the research, development, and application cycle and its efforts to coordinate research and development activities with other agencies. This report responds to this request and provides details on the amounts spent on research by health issue or disease, recipient, and stage of research or development funded.

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The results of USAID-supported research have had significant public health impacts, starting with Oral Rehydration Salts (ORS), now used in about 85% of child diarrhea cases in almost half the world's children under 5. The results of Vitamin A research now save approximately 1 million pre-school aged children a year. And, the impact of zinc, another USAID research product, on decreasing child mortality could be as or more significant than Vitamin A. By 2004, 2.5 billion auto-disable syringes and 900 million vaccine vial monitors, both results of USAID supported research, had been sold or distributed worldwide. USAID funded research has resulted in food fortification programs, making fortified sugar, cooking oil and flours available to the majorities of the population of many countries. More recently, USAID research on natural family planning has resulted in the development of two new methods, both of which have shown to be very effective when used correctly. USAID supported large-scale efficiency trials of insecticide treated nets across Africa, which provided definitive data on the highly effective impact of ITNs for preventing malaria among the most vulnerable populations of women and children. This report further details the impact of research in many other areas.

USAID invests in research to identify and assess key health problems affecting populations in developing countries and to develop and introduce new vaccines, tools, and approaches to help resolve these problems. The objective of almost half of USAID research activities is to find ways to "introduce" and make life-saving interventions accessible to those most in need -- children under five, mothers, people living with or at risk of HIV/AIDS and TB, and women and men of reproductive age. The other objectives of USAID research activities are to identify or assess major public health problems and develop a new tool or approach to help resolve these problems.

Other partners complement the different roles that USAID plays in the cycle from research to implementation. In some cases, for example, research to develop a malaria vaccine, the objective of US Government partners is different from that of USAID - a short term vaccine to protect troops versus a long term vaccine to protect vulnerable women and children. In the case of Oral Rehydration Salts and Vitamin A, USAID's role began with the identification of the problem and the development of the intervention, right up to wide scale introduction, working with WHO and UNICEF. USAID's research role in yet other cases is to provide information necessary to the private sector to carry out large scale commercialization of new products such as fortified foods and long-lasting insecticide treated bed nets.

USAID's role in the development of microbicides, for example, is to focus research and development on safe, effective and acceptable microbicides to prevent HIV infection that have the appropriate cost and product characteristics for use in developing countries and, in some cases, offer dual-protection as a family planning method. USAID collaborates with NIH, CDC, and FDA to develop the U.S. Government's Strategic Plan for Microbicides.

This report details research that USAID has supported and its results. In some of the newer areas of research the report also looks at ongoing studies. One example

Assessment, Development, and Introduction Research – Definitions

Assessment research includes problem identification and priority setting to determine the nature, determinants, or extent of a public health problem and whether it can be, should be, or already is being addressed. This can occur at any point in the research process.

Types of activities considered:

1. All formative research, baselines for interventions, specialized surveys of small target groups in preparation for interventions
2. Knowledge-attitudes-practices surveys
3. Meta-analyses and literature reviews aimed at identifying successful interventions
4. Surveys or assessments to determine the current state of a public health problem

Examples include research to identify perceptions of the poor of access, and barriers to access, to services of nongovernmental organizations; an assessment of child mortality and morbidity in Eastern Europe and Eurasia; and a contraceptive prevalence survey.

Routine surveys for data collection at the program level, such as Demographic and Health Surveys and overall program evaluations, were not considered research for the purpose of this report. For example, USAID provides approximately $400,000 each year to WHO to support global TB surveillance, including the collection and verification of TB surveillance data from countries throughout the world, and the production of the annual WHO Report Global Tuberculosis Control report. This activity is not included in this report.

Development research includes applied or operations research to create or improve tools, approaches, and interventions to address a known public health problem. This could include trials, pilot tests, and other activities to develop a product, approach, or methodology, and test its initial effectiveness. Examples include field trials of insecticide-treated mosquito nets (ITNs), field trials of the pneumococcal conjugate vaccine, and development research on microbicides.

Introduction research includes activities to facilitate the adoption or implementation of a proven intervention, tool, or approach in the field. At this stage, an intervention, approach, or tool already exists to address the given problem, but additional research may be needed to adapt it to and determine its effectiveness in the local context or to bring the intervention to scale. Research questions at this stage could include how to package or present a tool or approach to maximize its impact and adapt and introduce it into policy and programs in a developing-country context.

Types of activities considered:

1. Efforts to monitor/measure the effectiveness of a known intervention in the local context, such as research to monitor the effectiveness of the "community therapeutic care" approach
2. Activities seeking to determine obstacles to scale-up or to achieving maximum effectiveness, such as a survey of client experience with midwife-inserted intrauterine devices or research to determine the level and manner of ITN use in order to improve messages for increasing their use for malaria prevention
3. Introduction studies of a new contraceptive method and a NORPLANT or Jadelle implant
4. Conferences, workshops, meetings, and publications specifically geared toward disseminating research results or methodology

of these is a soon-to-be commissioned review by Brian Sharp, Medical Research Council, Durban, South Africa, and Christian Lengeler, Swiss Tropical Institute, Basel, Switzerland to compare indoor residual spraying (IRS) and insecticide treated nets (ITNs) across a range of malaria transmission settings in sub-Saharan Africa in terms of cost-effectiveness, impact on health measures, and operational constraints. The report, expected in early 2006 should provide clear, evidence-based guidance to National Malaria Control Programs and USAID missions on key factors to consider when selecting vector control interventions to ensure maximum public health effectiveness for money spent. Another example is the ongoing research on simple low-cost community care packages (warming, delayed bathing) that could reduce neonatal deaths by an average of 40 percent in low resource settings.

The research areas described in section I were selected because they account for the majority of USAID research and results over the past two decades. Some have resulted in USAID "signature" products such as vitamin A, oral rehydration solution and oral rehydration therapy, zinc supplementation, contraceptive technologies and safe injection technologies now used in countries throughout the developing world. Other areas – such as a malaria vaccine, an HIV/AIDS vaccine, and microbicides – are in earlier stages in the search for effective public health interventions.

The six research areas show how USAID's strategic involvement in research has contributed and will continue to contribute to viable cost-effective interventions that are relevant to low-resource settings and key public health needs. The six areas are:

1) Vaccine development (malaria vaccine, HIV/AIDS vaccine, rotavirus and pneumococcal conjugate vaccines, vaccine- and injection-related technologies)

2) Maternal, newborn, and child health interventions

3) Microbicides

4) Contraceptive technologies

5) Malaria

6) Tuberculosis

Although not directly addressed as a separate area, USAID invests in research on health system dynamics as part of each area in section I. Examples of this research include the adaptation and introduction of quality improvement approaches developed for the U.S. health system to developing-country settings and studies on what share of health spending on AIDS patients comes from their own families. USAID pioneered the development of national health accounts, a budgeting tool for estimating health expenditures now in wide use by governments and international organizations. Other examples are economic analyses of the costs of HIV/AIDS and of the returns to private firms on investments in HIV/AIDS prevention and treatment. South Africa's National Treasury Department is using this work to assess the potential costs and benefits of the national AIDS treatment program.

USAID has also abandoned certain areas of research, usually because they fail to produce the expected results or are picked up by other donors. Immunocontraception is an example of the former. From the mid-1980s to the 1990s, USAID, along with the National Institutes of Health and the World Health Organization, supported university-based scientists who were trying to develop contraceptive vaccines aimed at surface antigens, i.e., proteins that are found on the surface of sperm and eggs that when neutralized should prevent fertilization. This line of research was halted when it became evident that the likelihood of success was low; the potential risks and the costs of testing high; and the pathway for development and regulatory approval uncertain. Childhood vaccine development is an example of the latter, where research costs were high and other donors entered the field with sufficient funds to justify USAID's withdrawal while focusing its support more on implementation.

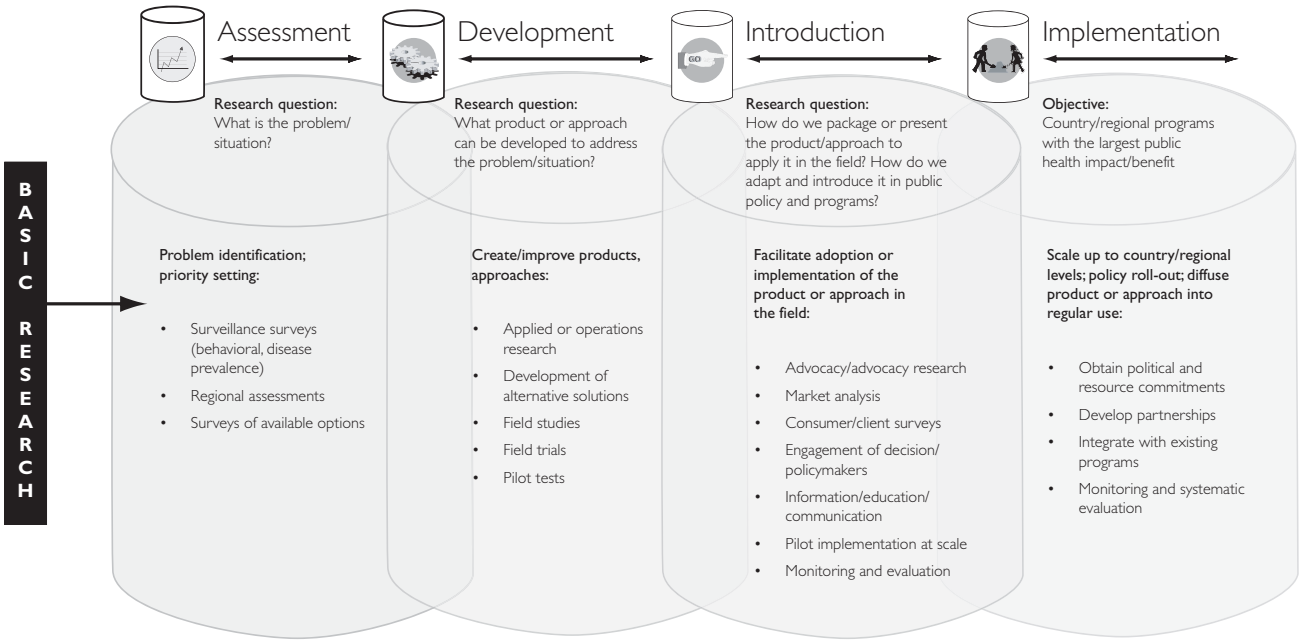
The Research Cycle and USAID's Research Roles: Figure I.1 illustrates the research-to-application cycle and USAID's research roles within it. Starting after basic research, (Basic Research, according to USAID coding is "The systematic study directed towards greater knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications toward processes or products in mind.)

which USAID generally does not support, assessment research, development research, and introduction research lead to the widespread application of evidence-based products, programs, services, and policies.

Assessment research identifies problems and sets priorities by asking, "What is the health problem?" Development research creates and improves products and approaches by asking, "What product or approach can be developed to address the problem?" Introduction research facilitates the adoption or implementation of the product or approach in the field by asking, "How best to package or present the product or approach in public health policy and programs?"

The information presented in section II employs the same categories – assessment, development, and introduction – to organize and present the data from the approximately 1,300 research entries between 2002 and 2004 collected and analyzed for this report.

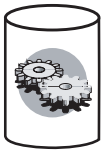
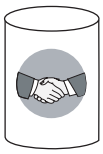
Figure 1.1 Research, Development, and Application Cycle



1. VACCINE DEVELOPMENT

Malaria Vaccine

Budget 2004	$6.2m
Since 1980	$147m

USAID Role in Research/Development/Application Life Cycle	
	**Development** Speed development of malaria vaccines to protect children and pregnant women from death and serious disease in malaria-endemic areas
	**Coordination** U.S. Department of Defense (Walter Reed Army Institute of Research; Naval Medical Research Center) National Institutes of Health; Centers for Disease Control and Prevention; Food and Drug Administration; Malaria Vaccine Initiative

USAID's Malaria Vaccine Development Program (MVDP) has been an integral part of U.S. government malaria vaccine research and development since the inception of the program. The research and development activities performed or supported by the Department of Defense (DOD) and USAID are largely responsible for the "state of the art" of malaria vaccine development today. The efforts of both agencies, which began some four decades ago, have been essential to bringing the field to its current promising state.

USAID has had a critical catalytic role in moving the current set of vaccine candidates through the research process to field trials. As a result of USAID's investments over the years, two vaccine candidates are currently undergoing safety or efficacy trials in the field.

The USAID objective in developing a vaccine is to help prevent the deaths of more than a million people each year in the developing world, mostly children and pregnant women. The DOD objective is to prevent the erosion of military capability due to malaria in military personnel, a phenomenon that has changed the outcome of many military engagements. Despite these two different objectives, the DOD/USAID collaboration has resulted in major progress toward products that respond to both objectives.

USAID initiated the MVDP in 1965. USAID's goal for the MVDP was to introduce cost-effective immunization into malaria control programs. The DOD malaria vaccine program also began in the 1960s in response to the rapid emergence of resistance to chloroquine, a drug the military depended on to prevent malaria in troops.

In the 1990s, the National Institutes of Health (NIH) in the Department of Health and Human Services (HHS) began a major malaria vaccine development initiative due in large part to the leadership of then NIH Director Harold Varmus. The initiative included both an intramural program (research conducted at NIH) and an extramural program implemented through support to private sector organizations. USAID's MVDP "jump-started" the intramural program through an interagency agreement to support collaborative research between the two agencies. Subsequently, NIH support increased dramatically, and USAID has not contributed financial support to the NIH program for a number of years. Collaboration, however, has continued.

In 2000, the Malaria Vaccine Initiative (MVI) at the Program for Appropriate Technology in Health (PATH) was initiated through a $50 million award from the Bill & Melinda Gates Foundation. Since then, MVI has become a robust partner of U.S. government agencies.

Examples of USAID coordination in malaria vaccine development follow:

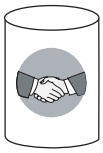
- In 1995, USAID initiated a program at the DOD Walter Reed Army Institute of Research (WRAIR) to develop vaccines against malaria blood-stage parasites. This effort complemented the liver-stage vaccine program already underway at WRAIR with GlaxoSmithKline (GSK) Biologicals. USAID continues to fund this program, which has resulted in the design, production, clinical testing, and initial field evaluation of two vaccines. Additional support of field testing of one vaccine has been provided by MVI in conjunction with USAID in Kenya and of the other by NIH in Mali. Two other vaccines will enter clinical trials at WRAIR in 2006.

- In 2004, USAID entered into a direct multiyear agreement with MVI which currently supports the Kenya field trial in addition to other activities.
- USAID funds the evaluation of DNA and adenovirus approaches to malaria vaccine development by the DOD Naval Medical Research Center (NMRC). The NMRC agreement allows USAID to invest in the development of other vaccine approaches, which will be needed if the vaccines currently in field trials do not prove to be effective. Through the agreement with NMRC, USAID can access these advanced approaches for the development of vaccines targeting children in the developing world. The approaches include (but are not limited to) the use of (1) vaccines administered through viral vectors (adenoviruses and pox viruses) or as plasmid DNA in various formulations; (2) "prime-boost" or "heterologous" immunization strategies; and (3) multi-antigen immunization. It is anticipated that these approaches will lead to clinical and field trials of vaccines that may prove to be more effective than the more conventional approaches already in progress.
- USAID supported the evaluation of vaccines in nonhuman primates by the HHS Centers for Disease Control and Prevention (CDC).
- USAID has supported an effort by Maxygen, Inc., in collaboration with the NIH, to apply its "molecular evolution" technology to create entirely new molecules which could be used in vaccines that would elicit a broader immunity against parasites of differing variant types than the molecules produced by the parasites. If successful, the technology would circumvent one of the most difficult aspects of malaria vaccine development, i.e., the development of a vaccine which would work against the many different variants that exist in nature. Maxygen will provide the final report of this effort in late 2005, which will provide an opportunity to assess the feasibility of the approach.

The U.S. government malaria vaccine development effort is facilitated by the Federal Malaria Vaccine Coordinating Committee (FMVCC), an informal group that provides a venue for information interchange that often has been the breeding ground for new collaborations. In addition to USAID, WRAIR, NMRC, and NIH, this group includes the Food and Drug Administration (FDA) and the MVI. Currently, the USAID MVDP staff member chairs the FMVCC.

HIV/AIDS Vaccine

Budget 2004	$24m
Budget 2003	$10.4m
Budget 2002	$10m

USAID Role in Research/Development/Application Life Cycle	
	**Development** Refocusing efforts on HIV/AIDS vaccines that are appropriate for developing countries; preclinical and clinical studies of vaccine candidates; building on USAID field presence and experience to strengthen capacity for trial sites and for introducing vaccines when they become available
	**Coordination** International AIDS Vaccine Initiative; Partnership for AIDS Vaccine Evaluation; Global HIV Vaccine Enterprise

USAID supports HIV/AIDS vaccine development through the global not-for-profit International AIDS Vaccine Initiative (IAVI). IAVI and its network of partners research and develop vaccine candidates. USAID funding accelerates the development and introduction of new vaccine candidates and technologies and helps link vaccine designers with manufacturers and developing-country sites suitable for testing promising HIV vaccine candidates. Through IAVI, USAID supports all phases of HIV vaccine research as well as policy analysis and other work to pave the way for introducing a vaccine when it becomes available.

Specifically, USAID support for IAVI encompasses:

- Designing and implementing preclinical and clinical studies of vaccine candidates
- Supporting IAVI's core immunology laboratory and primate facilities
- Building local capacity at trial sites
- Supporting preclinical development of HIV vaccine candidates
- Providing material preparation, sample analysis, and regulatory support for safety and feasibility clinical trials (phases I and II) of HIV vaccine candidates

IAVI has inspired a major shift in the HIV vaccine field, causing it to refocus its efforts on vaccines appropriate for developing countries. Prior to IAVI's formation, most HIV vaccine research was focused on HIV subtype B, which is primarily found in developed countries. IAVI also is committed to building capacity in the developing world and is collaborating with scientists in Kenya, Uganda, and South Africa to test vaccine candidates in clinical trials.

USAID is working with IAVI to explore how capacity building by IAVI for preparation of clinical trial sites in developing countries can be leveraged to support the roll-out of HIV/AIDS treatment, care, and prevention, especially under the President's Emergency Plan for AIDS Relief (PEPFAR). Conversely, new HIV/AIDS treatment programs can be beneficial for large-scale vaccine trials. During the enrollment period of phase III (efficacy) vaccine trials, it is likely that large numbers of people will be screened who are in immediate need of antiretroviral therapy. Having convenient treatment available and appropriate referral mechanisms in place will help the trials ensure positive relations with the communities where they are conducted.

USAID also participates in the Partnership for AIDS Vaccine Evaluation (PAVE), a voluntary consortium of U.S. government agencies and key U.S. government-funded organizations involved in the development and evaluation of HIV/AIDS preventive vaccines and the conduct of HIV vaccine clinical trials. The goal of developing a safe and effective HIV vaccine is one that no single entity or institution is likely to accomplish on its own. U.S. government partners in PAVE include the Division of AIDS (DAIDS) of NIH's National Institute of Allergy and Infectious Diseases (NIAID); the Dale and Betty Bumpers Vaccine Research Center (also NIAID); the DAIDS HIV Vaccine Trials Network; the

NIH Office of AIDS Research; the NIH AIDS Vaccine Research Working Group; USAID; CDC; and the DOD's U.S. Military HIV Research Program.

USAID also supports the idea of the Global HIV/AIDS Vaccine Enterprise (GHAVE) and would like to become more involved as it unfolds. Initially proposed by an international group of scientists, the GHAVE concept is analogous to the successful alliance and strategic plan that characterized the Human Genome Project. IAVI's chief executive officer is on the GHAVE Coordinating Committee. GHAVE recently published a strategic plan, but its organizational structure has yet to be determined.

Childhood Vaccines: Rotavirus and Pneumococcal Conjugate Vaccines

Funding to Date $1.4m

USAID Role in Research/Development/Application Life Cycle	
	**Development** Technical oversight for clinical trials of refined rotavirus vaccine and large-scale clinical trial of pneumococcal conjugate vaccine
	**Introduction** Supported selection of both vaccines by the Global Alliance for Vaccines and Immunization for undertaking a new approach to accelerated vaccine introduction in developing countries
	**Coordination** World Health Organization; National Institutes of Health; Centers for Disease Control and Prevention; GlaxoSmithKline; Centre for Health and Population Research of the International Centre for Diarrhoeal Disease Research, Bangladesh; Johns Hopkins University; Medical Research Council (London and the Gambia); London School of Hygiene and Tropical Medicine; Wyeth Lederle Vaccines; Program for Appropriate Technology in Health; Global Alliance for Vaccines and Immunization; Bill & Melinda Gates Foundation

Vaccines tested in children in the United States may not have the same effect in children in developing countries because of malnutrition and different disease profiles. Without the efforts of donors to leverage the associated risks of vaccine research development for developing countries, the private sector is less likely to make investments.

Rotavirus Vaccine: Rotavirus is the most common cause of severe dehydrating diarrhea and causes an estimated 500,000 deaths of young children each year, mainly in developing countries. By the mid- to late

1990s, Wyeth Lederle's FDA-approved Rotashield vaccine was commercially available in the United States and Western Europe. To facilitate its use in developing countries, USAID supported trials in Peru and Bangladesh that demonstrated the vaccine was even more effective in children in developing countries than in American children. Unfortunately, the vaccine was withdrawn from the market because of concerns that a small proportion of American children might experience intussusception, an adverse health outcome.

In response to Rotashield's removal from the market and in recognition that new vaccine development could take 10 to 15 years, USAID helped set up the Rotavirus Vaccine Action Partnership for Introduction and Development (RAPID), a partnership of U.S. government agencies, the World Health Organization (WHO), PATH, the Centre for Health and Population Research of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), and other developing-country researchers. The partnership approached a number of pharmaceutical companies and ultimately engaged GlaxoSmithKline (GSK). RAPID funded and provided technical oversight for clinical trials of the refined vaccine in South Africa and Bangladesh to determine if it was safe and effective in children who needed it most. This work is ongoing, with NIH, CDC, and PATH providing technical support and co-funding for the trials and GSK providing the vaccine and additional technical support.

GSK's investment in a rotavirus vaccine candidate and the accelerated vaccine testing process would not have been possible without the preliminary work, supported by USAID, of the ICDDR,B Centre for Health and Population Research in testing the human rotavirus candidate vaccine in the early 1990s. GSK initially was only interested in testing the vaccine for use in developed and middle-income countries, but, thanks to the RAPID partnership, agreed to cooperate in the South Africa and Bangladesh trials.

The RAPID partnership also has stimulated other vaccine manufacturers to test promising rotavirus vaccine candidates in developing countries. If a vaccine can be used effectively and safely in both middle-income and developing countries, and as other pharmaceutical companies enter the market, the chance increases that an affordable and sustainable vaccine can be introduced at low cost in the poorest countries of the world.

Pneumococcal Conjugate Vaccine: Pneumococcus infection affects the elderly and the very young and is estimated to cause 1.6 million deaths every year, half of them in children under age 5. Wyeth Lederle is the only manufacturer of pneumococcal conjugate vaccine, which is effective in children and the elderly in the United States and Western Europe.

In the 1990s, USAID joined a broad coalition of international partners, including the NIH, the Medical Research Council (London and the Gambia), the London School of Hygiene and Tropical Medicine, the Gambian Ministry of Health, WHO, CDC, Wyeth Lederle, and PATH, to undertake a large-scale clinical trial in the Gambia. In partnership with WHO, USAID's role was to catalyze and coordinate the research partnership. The trial's recently published results appear promising – for each 1,000 children immunized, approximately six lived who otherwise would have died from streptococcus pneumonia.

A USAID immunization team oversees the congressional appropriation to the Global Alliance for Vaccines and Immunization (GAVI) and its Vaccine Fund (nearly $300 million dollars since 2001). GAVI has selected rotavirus and pneumococcal disease as the two focus diseases for undertaking a separate and novel approach to accelerated vaccine development and introduction in developing countries. These activities were given a three-year mandate and a budget to:

- Define disease burden data and specific seroprevalence information
- Educate decision-makers about the diseases and their respective death rates
- Support further trials as needed
- Begin mapping and discussing vaccine supply and pricing issues with producers while considering financing options for developing countries over time

Vaccine- and Injection-Related Technologies

Funding to Date $4.30m

USAID Role in Research/Development/Application Life Cycle	
	**Development** Identified need for technologies to prevent syringe and needle reuse and to monitor condition of field vaccines; launched program to develop devices to meet these needs
	**Introduction** Support for auto-disable syringes and vaccine vial monitors now in widespread use in developing-country immunization programs
	**Coordination** Program for Appropriate Technology in Health; World Health Organization; United Nations Children's Fund; Becton, Dickinson and Company; Pfizer Inc.; Global Alliance for Vaccines and Immunization

Auto-Disable Syringes: In 1987, a decade before the international public health community mobilized around the problem of frequent reuse of contaminated needles and syringes, USAID identified the need for technologies that could prevent such reuse. Working with PATH through the USAID-supported HealthTech program, USAID launched a program to develop and introduce the devices now known as auto-disable (AD) syringes.

By the early 1990s, two suitable AD technologies had been developed, evaluated in the field, licensed to a major syringe manufacturer, and produced in pilot quantities. One of them – the SoloShot™ syringe* – was one of the first feasible approaches to nonreusable syringes for immunizations. USAID funded John Snow, Inc., to carry out the first validation tests of the device in Pakistan under the direct observation of WHO. These successful field trials led to scale-up, production, and introduction of the first commercial AD syringe for immunizing children. WHO accepted the field trial results, endorsed the technology and, with the United Nations Children's Fund (UNICEF), issued a policy to recommend and supply AD syringes instead of standard disposable syringes for all immunizations. In 1996 alone, 56 million AD syringes were distributed by UNICEF, primarily for immunization campaigns. In 1999 distribution for that year increased to 150 million.

Alternative AD syringe designs became available in the latter half of the 1990s, encouraged and facilitated by USAID and its partners. Competitive forces and growing worldwide use have cut the price of AD syringes in half, which has led to a general adoption of AD technologies by GAVI and many governments and agencies around the world. AD syringes now are improving the safety of routine immunizations as well as the safety of injectable contraception and a growing number of curative procedures. Since their commercial introduction in 1992, more than 1 billion SoloShot syringes have been supplied to public health programs in more than 40 countries in Africa, Asia, Eastern Europe, and Latin America. UNICEF – which has already distributed hundreds of millions of AD syringes to immunization programs – now provides only AD syringes (many of them SoloShot) to countries requesting disposable syringes. It is anticipated that the transmission of bloodborne diseases due to dirty needles will be reduced by 90 percent in programs using these products.

In the last year, USAID- and CDC-funded projects have been able to procure and supply 12 of the 15 PEPFAR focus countries in Africa and the Caribbean with more than 15 million safety syringes for use in curative care.

USAID supported another version of the AD syringe, the Uniject™ injection device.* (see Figure 1) Uniject is a unique pre-filled, single-use syringe with needle attached. The device was invented and developed with USAID funding starting in 1987. In collaboration with the licensee, Becton, Dickinson and Company (BD), the world's largest manufacturer of injection equipment, USAID and PATH carried out all the steps of product development and field trials. BD now commercially

* SoloShot and Uniject are trademarks of Becton, Dickinson and Company.

produces and distributes the device to drug and vaccine manufacturers.

The Uniject device can be used to expand safe immunization coverage in several ways. As an AD syringe it cannot be reused. Traditional birth attendants (TBAs) can use it to immunize hard-to-reach children and women in their communities. Multidose vial waste is eliminated, saving precious dollars, since a Uniject device contains a single dose of vaccine. In addition, the single-dose format overcomes some health workers' objections to opening a multidose vial for a single child, thus ensuring that each child receives a dose of vaccine regardless of the size of the immunization session.

UNICEF has identified Uniject as an important tool in its efforts to eliminate maternal and neonatal tetanus in high-risk areas around the world. By allowing TBAs to deliver safe injections, Uniject is especially effective in reaching women who previously have not been immunized due to ethnic or religious barriers or limited health infrastructure.

USAID also has been active for many years in improving the safety of medical waste disposal and in promoting the "bundling" of injectable contraceptives, disposable syringes, and medical waste safety disposal boxes for use in USAID-supported family planning programs. More recently, USAID advocated for the use of the Uniject device as a packaging and delivery option for injectable contraceptives. USAID is working toward that goal in partnership with PATH, BD, and Pfizer Inc., the dominant supplier of injectable contraceptives for USAID programs.

Safe Disposal Methods: One challenging outcome of the increased use of AD syringes is the increased volume of medical waste in the form of used syringes and needles. Infectious sharps waste is dangerous to health care workers, waste handlers, and the community. Therefore, safe disposal methods for sharps are needed to protect anyone who may come in contact with contaminated needles.

USAID has been supporting the development and advancement of technologies that health workers can use to safely dispose of used needles and syringes. These include safety boxes and needle removers to separate the used and possibly contaminated needles from the syringe for easier disposal. These approaches reduce and contain the volume of hazardous waste. These waste technologies currently are being procured and used widely in the PEPFAR focus countries in conjunction with AD syringes. Needle removers already are in wide use in immunization programs, including India's, and WHO has included needle removal as a safe disposal option in health care waste management plans for sub-Saharan Africa.

Vaccine Vial Monitors: For nearly 20 years, USAID has been involved in developing technologies to improve vaccine quality by limiting the adverse effects of excessive heat and freezing. Vaccines require careful storage and transport to the point of use to avoid harmful heat exposure or freezing temperatures. In the past, because there was no way to detect whether individual vials had been exposed to heat at some point during storage or transport, national immunization programs adopted conservative guidelines for vaccine handling and disposal when heat exposure was suspected.

In 1987, USAID launched a search for suitable technologies that could identify exposure to heat. An appropriate technology developed for the food industry was discovered. USAID and its partners worked with the manufacturer to adapt it for vaccines. The result was the "vaccine vial monitor" (VVM), a small circular indicator printed directly on vial labels, or fastened to the tops, that changes color irreversibly from light to dark with exposure to heat over time.

Since their introduction in 1996, VVMs have helped ensure that only potent vaccine is used to immunize children. The presence of VVMs made it possible for the polio eradication campaign to carry oral polio vaccine safely into remote areas without refrigeration. It also enabled WHO to implement a multidose vial policy that allows health workers to use opened vials of vaccine for more than one day. Since January 2001, UNICEF has required that all its vaccines have VVMs. To date, more than 1 billion vaccine vials with VVMs have been delivered to developing countries. Sixteen United Nations prequalified vaccine suppliers currently include VVMs on their products.

In addition to AD syringes and VVMs, other

Table I.1. Results of USAID-Supported Vaccine- and Injection-Related Technologies

Technology	USAID Investment (Since 1987)	Private Sector Partner	Coinvestment Amount	Units Sold/ Distributed Worldwide as of 2004
AD Syringes (SoloShot)	$284,000	Becton Dickinson	$15,000,000 +	2,500,000,000
Vaccine Vial Monitors	$988,000	TempTime (ex-LifeLines Technologies)	$1,500,000+	904,000,000
Uniject Injection System	$3,032,000	Becton Dickinson	$35,000,000+	43,000,000

technological solutions to constraints on immunization programs include needle-free jet-injector devices that can be used for giving injections without needles and thermostable vaccines that will not require refrigeration. Such products are under development.

Figure I

The Uniject injection device is a pre-filled syringe with needle attached that cannot be re-used.

2. MATERNAL, NEONATAL, AND CHILD HEALTH INTERVENTIONS

Maternal and Neonatal Health

USAID Role in Research/Development/Application Life Cycle	
	**Assessment** Meta-analyses of impact of iron-deficiency anemia on maternal mortality and impact of skilled birth attendants on safe delivery; current practices in management of the third stage of labor; literature review of causes of maternal mortality; cost-effectiveness of interventions to reduce maternal and perinatal mortality; relationship between cesarean section and pregnancy outcomes
	**Development** Wide variety of technologies and approaches in such areas as anemia detection and prevention, antenatal care, safe delivery, maternal and infant care; testing of models of antenatal and neonatal care
	**Introduction** Support for Safe Birth Kits and maternal health record now in use throughout the world; expanded anemia prevention and control programs; evaluation of intervention strategies to improve maternal and perinatal health and studies of barriers to use of iron supplements; implementation of new models of antenatal and neonatal care and payment schemes to enable poor women to obtain maternal care and skilled care at delivery
	**Coordination** Program for Appropriate Technology in Health; World Health Organization; United Nations Children's Fund; National Institute for Medical Research; Tanzania Ministry of Health; London School of Hygiene and Tropical Medicine; Instituto de Investigacion Nutricional, Peru; Johns Hopkins University;
	**Coordination (continued)** University of Indonesia; College of Medicine, Malawi; Project HOPE; Project Concern International; St. John's Medical College, India; Survival for Women and Children Foundation of India; Baroda Citizens Council, India; Rural Unit for Health and Social Affairs, Christian Medical College and Hospital, India; John Snow, Inc.; Khon Kaen University, Thailand; American College of Nurse Midwives; Save the Children; University Research Corporation; the Futures Group; Abt Associates; University of Aberdeen; the Institute of Tropical Medicine, Antwerp; Centre Muraz, Burkina Faso; Noguchi Institute, Ghana; Centre for Family Welfare, University of Indonesia, Aga Khan, All India Institute of Medical Sciences

Since the launch of the worldwide Safe Motherhood Initiative in 1987, USAID, working with a broad range of partners, has supported the development and testing of new technologies and community and facility approaches, as well as meta-analyses of research, to improve and transform maternal and neonatal health interventions.

New Technologies and Approaches: USAID-supported research has resulted in the following new technologies and approaches:

Visual anemia scale: This simple color scale matches up with a drop of blood absorbed on special paper. It enables front-line health workers to detect basic levels of hemoglobin without laboratory equipment and increase iron supplementation or make a referral, depending upon the severity of anemia.

Home-based maternal record: This record is kept by mothers and filled in at each care visit to the home. It records basic information about the mother and infant, health complications, and treatment. The prototype record was tested extensively and over the years has been translated and adapted throughout the world.

Safe Birth Kit: This kit was developed to promote clean delivery practices at home. It includes pictorial instructions, a small bar of soap, a polyethylene delivery sheet,

a cord-cutting surface, cord ties, and a clean razor blade. Research in Nepal showed that the Safe Birth Kit had a positive impact on reducing cord infections in newborns. Research in Tanzania showed that the kit, coupled with an educational intervention, was strongly and significantly associated with lower incidence of cord infections and puerperal sepsis.

Promotion of iron consumption: Anemia is both a direct and indirect cause of a substantial portion of maternal mortality and disability. Iron deficiency is the most common cause of anemia and is amenable to prevention and treatment with iron supplements. USAID-supported operational studies have uncovered many consistent barriers to optimal use of iron supplementation. Studies in Malawi, India, Peru, and Indonesia, for example, demonstrated that supply, rather than side effects, is often the problem. Behavior change for increased supplement consumption can be achieved by both adolescents and adult women through a variety of approaches, including education in community kitchens (Peru), side effects management (Malawi), links to premarital counseling (Indonesia), and improved nutritional awareness and supplement supply and distribution (India).

Streamlined antenatal care: A randomized controlled trial was carried out in Thailand as part of a larger multicenter study of a traditional versus a streamlined approach to antenatal care (ANC). It tested for maternal morbidity, perinatal morbidity and mortality, satisfaction, and cost. The streamlined approach to ANC emphasizes essential elements of care that have been demonstrated to affect pregnancy outcomes and is now informing programmatic approaches and service indicators throughout the world.

Family-centered maternity care: A family-centered maternity care model emphasizing family education about childbirth, family involvement in decision-making, and discouragement of unnecessary technology use was tested in Ukraine. The experiment resulted in cost savings for families, decreased use of cesarean section, increased birthweight, virtual elimination of newborn hypothermia, and no documented increase in adverse outcomes. The program has been expanded to other areas of Ukraine and to Russia.

"Auto diagnosis" in communities: A participatory "auto diagnosis" process was developed and tested in isolated mountain communities of Bolivia. Women's groups were organized and assisted in holding discussions to explore maternal and neonatal health problems. Following the intervention, there was a documented increase in family planning and a decrease in perinatal mortality. This model (known as the Warmi model) has been adopted more broadly in Bolivia and adapted to other countries.

Quality of care: A new job aid, the care management map (CMM), was developed and tested successfully in Russia to define sequencing and timing of key interventions. The CMM successfully promoted adherence to standards of care for clients admitted to a hospital with pregnancy-induced hypertensive disorder.

Paying for services: Throughout the world, health care fees deter the use of lifesaving skilled care at delivery. Poor families typically lack funds to pay for high and often unpredictable maternity care fees. A multicenter study in Peru, Kenya, Egypt, Vietnam, and India documented low utilization levels of maternal health services among poor women. Women in all five countries demonstrated poor knowledge of waiver and exemption mechanisms, an important finding that can be used to increase knowledge in the community and save lives. In Rwanda, where less than one-third of all women deliver their babies with the assistance of a health professional, a prepaid insurance plan was found to increase the use of medical services.

Meta-Analyses: Meta-analyses of research findings include:

Traditional birth attendant (TBA) training: The meta-analysis (cofunded with the World Bank) showed an uncertain association between TBA training and maternal mortality reduction due to insufficient data caused by a shortage of studies and incomplete reporting. This meta-analysis provided additional information about the statistical association between the skilled birth attendant and maternal mortality reduction, which led to a paradigm shift in emphasis away from TBA training toward promoting the presence of skilled birth attendants at delivery in order to achieve a decline in maternal mortality. The analysis did show a statistically significant

association between TBA training and peri/neonatal mortality reduction, supporting the use of community workers for newborn care.

Iron-deficiency anemia: Iron-deficiency anemia affects 55 percent of pregnant women in developing countries. A meta-analysis of prospective observational studies found it was an underlying risk factor in 20 percent of maternal deaths attributed to other causes. This finding provides a basis for increasing the resolve of nations to promote robust anemia prevention and control programs.

Ongoing research and meta-analyses: The subjects of ongoing studies include:

- Current practices in management of the third stage of labor
- Causes of maternal mortality literature review
- The cost-effectiveness of interventions to reduce maternal and perinatal mortality
- The relationship between cesarean section and pregnancy outcomes in the Global Data System
- An evaluation of intervention strategies to improve maternal and perinatal health and survival

Oral Rehydration Salts, Oral Rehydration Therapy

USAID Role in Research/Development/Application Life Cycle	
	**Development** Early formulations of oral rehydration salts (ORS) for treating diarrhea in young children in 1960s and '70s and development of oral rehydration therapy (ORT) – the use of ORS plus breastfeeding for infants and ORS plus fluids and supplemental feeding for older children; development of improved ORS formulation in late 1990s
	**Introduction** Support for wide implementation of ORS/ORT for child diarrhea; between 1990 and 1995, use of ORS (or recommended home fluids) increased from 33 percent of child diarrhea cases to 85 percent in 33 countries containing almost half the world's children under age 5
	**Coordination** World Health Organization; United Nations Children's Fund; Johns Hopkins University; Harvard University; Boston University; Tufts University/New England Medical Center; Academy for Educational Development; Futures Group; Population Services International; host governments; developing-country research, social marketing, and implementation partners including the All India Institute of Medical Sciences, University Federal da Bahia (Brazil), Children's Hospital #1 (Vietnam), Hospital Nacional Cayetano Herdia (Peru), International Centre for Diarrhoeal Disease Research, Bangladesh, and many others

Diarrheal diseases are one of the leading causes of infant and young child deaths in less-developed countries. Since the 1960s, USAID-supported research has been instrumental in developing, refining, introducing, and stimulating the widespread use of oral rehydration salts (ORS) and later oral rehydration therapy (ORT)* to treat dehydration caused by diarrhea. Prior to research that proved that dehydration could be treated by ORS/ORT, dehydration was treated by intravenous infusion therapy, a riskier and more expensive treatment that is typically available only in health facilities.

USAID first supported research by scientists at the ICDDR,B Centre for Health and Population Research. This research resulted in the development and testing of a simple sugar and salt solution, which, when administered orally, provided safe treatment for most cases of severe dehydration. This formulation became known as ORS and with support from USAID cooperating partners and other donors became the first cornerstone of the WHO/UNICEF Program on Control of Diarrheal Diseases.

One of the first applications of ORS was its use in the 1970s in the mass treatment of cholera during a complex emergency in Asia. A decade later, working in partnership with WHO and UNICEF, USAID-supported researchers demonstrated that administering ORT early in the course of a diarrhea episode prevented dehydration and shortened the length of the episode, thereby helping to prevent malnutrition.

Working closely through the 1980s and 1990s with WHO, UNICEF, universities, NGOs, and private firms, USAID supported research and social marketing projects such as the Applied Diarrheal Disease Research, Pritech, and Healthcom projects. These efforts helped create the evidence base for understanding behavioral and care-seeking patterns and for developing the most effective behavioral change strategies to promote and make ORS and ORT available in developing countries. The widespread global adoption of ORS and ORT was certainly a major contributor to the decline in diarrheal disease-related mortality in children from 4.6 million deaths in 1980 to 3.2 million deaths in 1990.

By the 1990s, home management of child diarrhea had improved dramatically. In 33 countries containing almost half the world's children under age 5, use of ORS

* Oral rehydration therapy (ORT) is the combination of oral rehydration salts (ORS) with breastfeeding in infants and with available home fluids and supplemental feeding in older children.

or recommended home fluids increased from about 33 percent of child diarrhea cases in 1990 to 85 percent by mid-decade. Economic studies demonstrated that an estimated 1 billion dollars per year could be saved worldwide by treating diarrhea with ORT and eliminating useless and potentially harmful drugs. ORS is manufactured in most developed and developing countries and purchased by UNICEF and many developing-country governments for use in public health facilities. In a growing number of countries, families are able to obtain ORS free from public sector facilities or purchase this inexpensive treatment (approximately 10 cents) as an over-the-counter treatment.

Despite these advances, an estimated 1.5 million diarrhea-related deaths continue to occur every year. USAID has worked with WHO, ICDDR,B, and other research partners to develop the use of ORS in rehydrating severely malnourished children. USAID has also supported WHO and other research partners in refining the ORS formulation. The new formulation, called reduced-osmolarity ORS, further reduces the need for intravenous therapy and is safe for treating both children and adults. UNICEF and WHO have adopted the new formulation as the global standard. UNICEF now exclusively procures the new ORS, and many host governments, including India and Indonesia, mandate that their domestic manufacturers exclusively produce the new formulation.

USAID is no longer a major purchaser of ORS. To expand ORS/ORT use, USAID now invests as needed in social marketing efforts focused on consumer education. A recent USAID-supported social marketing campaign in nine northern states in India with high child mortality yielded significant results, increasing the availability of the WHO ORS formulation from 23 percent of pharmacist/chemist outlets in 2001 to 63 percent in 2003. Over the two-year program, sales increased by 62 percent and use of ORS (all varieties) to treat children with diarrhea increased from 26 percent to 50 percent.

Micronutrients: Zinc

Funding to Date $10m

USAID Role in Research/Development/Application Life Cycle	
	**Development** Research and roll-out of zinc supplementation as treatment for childhood diarrhea
	**Introduction** Product supply; guideline development; program planning; pilot testing; marketing research
	**Coordination** World Health Organization; Johns Hopkins University; Centre for Health and Population Research of the International Centre for Diarrhoeal Disease Research, Bangladesh; United Nations Children's Fund; Aga Khan University, Pakistan; All India Institute for Medical Sciences; University of Bamako, Mali; King George's Medical University, India; University of the Philippines; Save the Children; International Rescue Committee; Helen Keller International; Medical Care Development International; Project Hope; World Vision

The importance of zinc as an essential micronutrient for immune function, growth, and development was discovered in the 1960s. Scientists did not begin to understand the role of zinc in child health, however, until the 1980s, when researchers began focusing on zinc loss during diarrhea and zinc supplementation as treatment. Through ongoing collaboration with WHO, the Johns Hopkins University Bloomberg School of Public Health, ICDDR,B, partner universities abroad, and international NGOs, USAID has supported the critical research and programmatic roll-out of zinc supplementation for treating diarrhea.

In 1996, USAID convened a meeting of leading researchers and international health policymakers to summarize what then was known about zinc as a therapy and preventive nutritional supplement and to develop a research agenda. This meeting resulted in a target agenda and highlighted the need for two meta-analyses to summarize the trial data on zinc for diarrhea treatment and prevention. The two meta-analyses were published in 1999 and 2000. Following a structured research agenda, USAID has supported additional studies on the:

- Efficacy and safety of zinc treatment for diarrhea in young infants at the facility level
- Effectiveness of zinc as a diarrhea treatment provided at the community level and for reducing future morbidity and diarrhea-related mortality
- Acceptability of zinc when recommended as part of diarrhea treatment
- Efficacy of zinc supplementation in preventing diarrhea, acute respiratory infections, malaria, and growth retardation in many diverse populations (ongoing studies)
- Efficacy of zinc in treating pneumonia (ongoing)
- Efficacy of zinc and potential problems of interaction when combined or administered with other micronutrients

Figure I.2. Diarrhea Management with Therapeutic Zinc and Reduced-Osmolarity ORS: Phases of Intervention

Advocacy	Introduction	Expansion
Afghanistan		
Cambodia		
Ethiopia	Nepal	
Haiti	DR Congo	
Madagascar	India	
Nepal	Mali	
South Africa	Pakistan	
Tanzania	Sudan/Darfur	Bangladesh

Phase of Intervention

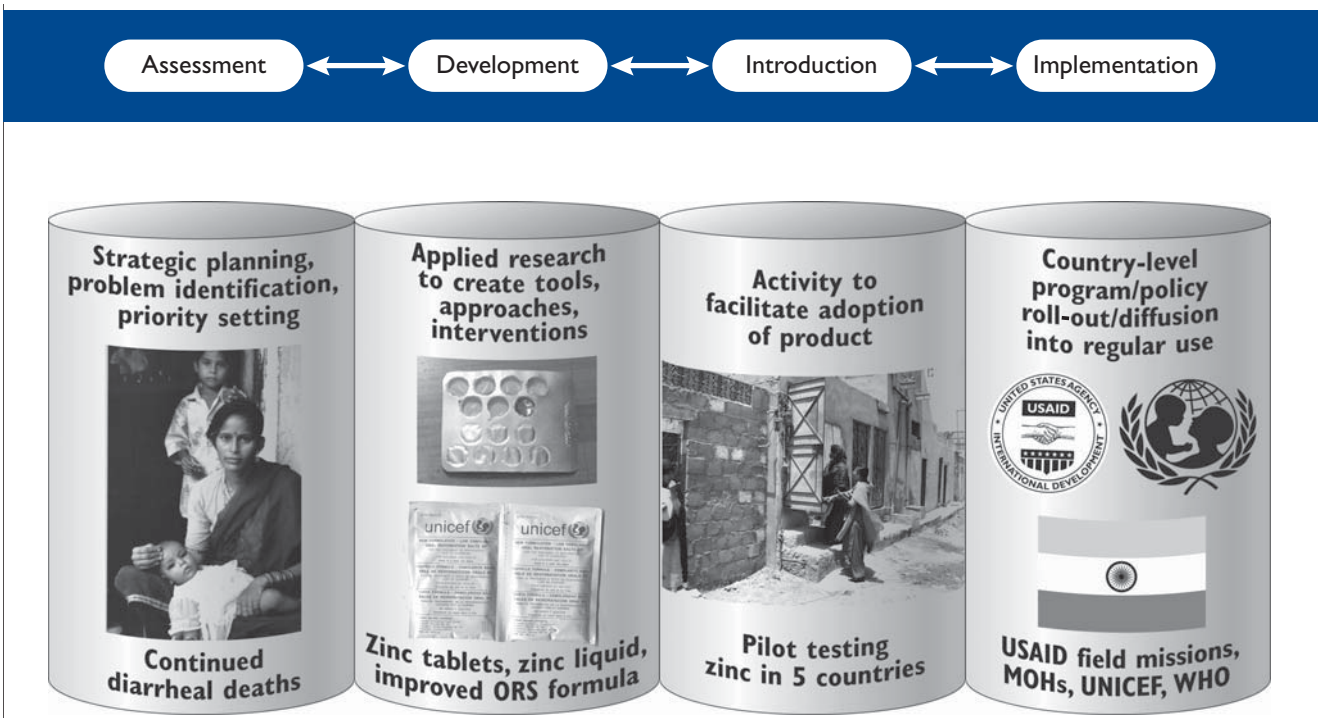
- Safety of zinc supplementation among children with HIV infection
- Effect of zinc supplementation on vaccine efficacy

These studies have taken place in countries where child health is in dire need of improvement, such as India, Bangladesh, Mali, and Ethiopia. Though all studies are not yet completed, the results of completed studies have been widely disseminated in more than 40 published reports and peer-reviewed journals. Results on the preventive use of zinc are anticipated within the coming year.

USAID-supported research built the evidence base that led to a joint statement by WHO and UNICEF recommending 10 to 14 days of zinc treatment, in conjunction with ORS and ORT, for treating all cases of diarrhea in children between 2 months and 5 years of age. This recommendation is based on the finding that treatment with zinc and ORS/ORT reduces the duration and severity of diarrhea episodes. Additionally, zinc treatment prevents future episodes of diarrhea for a two- to three-month period. Based upon a review by an external advisory committee, WHO has recently added zinc to its Model Essential Medicines List, a sign that zinc has fulfilled the conditions of efficacy and safety for diarrhea treatment. This also signals to governments that they should incorporate zinc treatment in their diarrhea management guidelines for public sector facilities and that drug regulatory authorities should enable private sector manufacturers or importers to make appropriate zinc products commercially available.

In partnership with WHO, UNICEF, NGOs, and other collaborating agencies, USAID is supporting work to translate the research findings into programs. This effort includes working with host governments to increase awareness and accelerate the adoption of the new recommendations for diarrhea treatment, as well as working on issues of product supply, guideline development, program planning, and marketing. As part of this process, USAID and U.N. agencies have supported the development of zinc formulations by manufacturers in a way that ensures thermostability in hot weather environments and under poor storage conditions. Another challenge has been to come up with a formulation that does not lead to vomiting, which is typically attributed

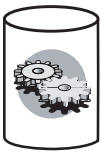
Figure I.3. Zinc as Diarrhea Treatment: USAID Research/Development/Application Cycle



to zinc's metallic taste. This can be averted with a high-quality product that masks the taste and has a long shelf life, whether in liquid or tablet form. In the coming year, USAID anticipates that a number of host governments will incorporate zinc into public health programs, both through clinics and extension workers, and will allow zinc treatment to become available in the private sector as an over-the-counter treatment.

Micronutrients: Vitamin A

Funding to Date $150m

USAID Role in Research/Development/Application Life Cycle	
	**Assessment** Studies of the epidemiology and health consequences of vitamin A deficiency on child, infant, and maternal health
	**Development** Large-scale clinical trials to develop evidence base to support vitamin A supplements for children, newborns, and pregnant women; clinical trials of impact of vitamin A treatment on reducing measles mortality, early infant mortality; confirmatory trials to assess the health benefits to the mother, fetus, and infant of maternal low-dose vitamin A supplementation
	**Introduction** USAID-funded cost-effectiveness research has established a strong case for vitamin A supplementation as the centerpiece of child survival activities. USAID also supports its collaborating scientists in laying the "advocacy" groundwork in the antenatal care and obstetrics/gynecology communities to bring increased attention to maternal nutrition as a complement to emergency obstetric care practices in improving maternal health and survival.
	**Coordination** World Health Organization; United Nations Children's Fund; Canadian International Development Agency; Johns Hopkins University; International Vitamin A Consultative Group; collaborating centers or ministries of health in Indonesia, Nepal, India, Sudan, Ghana, Bangladesh, Zambia

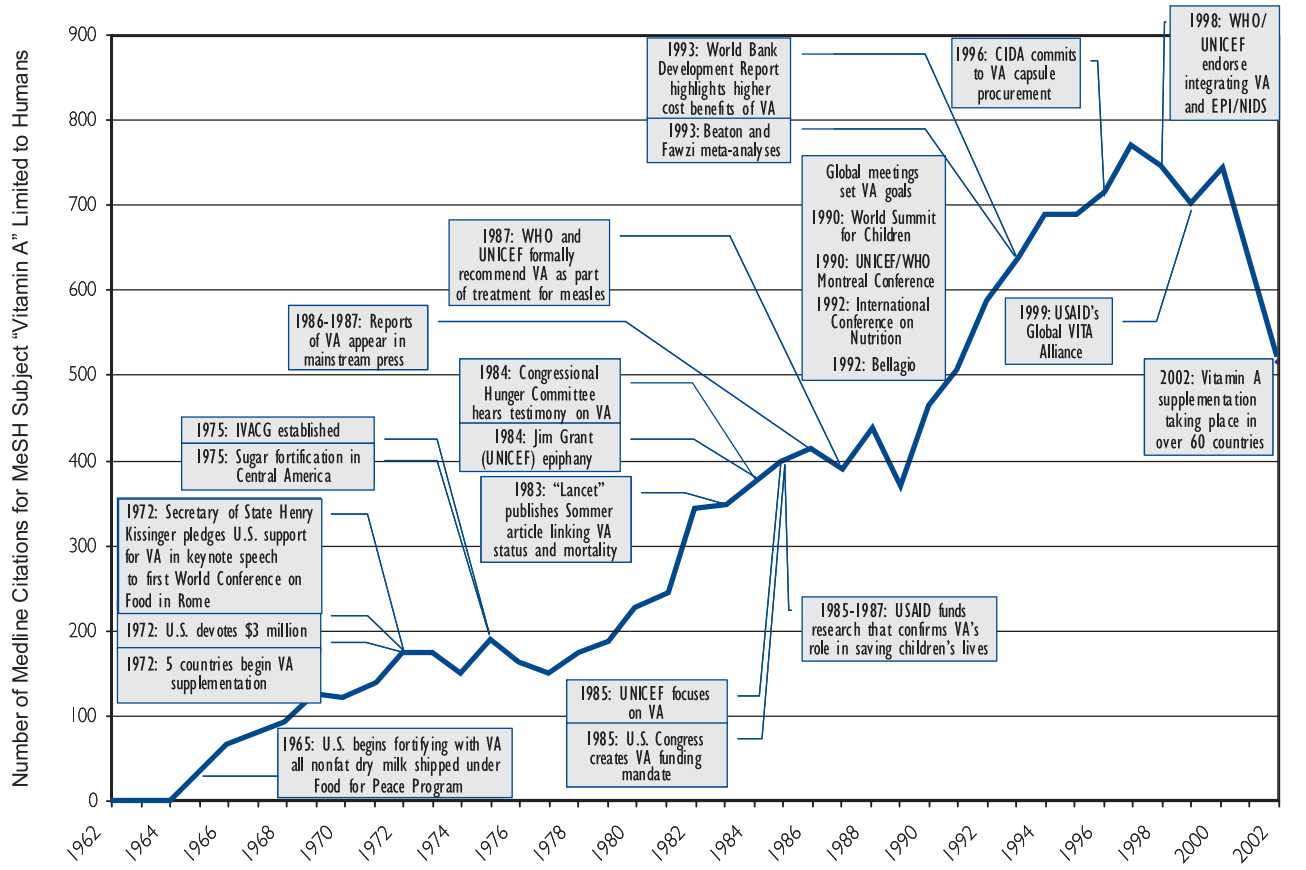
In 1974, USAID launched the world's first global strategy to combat micronutrient malnutrition in the

developing world. This strategy responded to a U.S. government commitment made at the World Food Conference to prevent childhood blindness due to vitamin A deficiency. In the three decades since, USAID has funded an innovative, systematic, and coordinated "research to policy to programs" micronutrient strategy.

Indonesia was the first country where global partners worked closely with the government to study the epidemiology and health consequences of vitamin A deficiency. This culminated in the discovery that two cents worth of vitamin A, given to children every six months, could reduce child mortality by 34 percent. Driven by the need for an adequate evidence base to drive policy, additional major trials were carried out in Indonesia, Nepal, India, Sudan, and Ghana. These trials were mostly funded by USAID, with assistance from other donors. Parallel to and in support of the above field studies, clinical trials funded by USAID and other donors found that vitamin A treatment also could reduce measles mortality by 50 percent or more. Vitamin A is now standard treatment for severe measles throughout the world. Vitamin A also reduces the severity of other illnesses, including diarrhea and malaria, both leading childhood killers in the developing world. UNICEF, with procurement largely funded by the Canadian International Development Agency, now delivers 600 million to 800 million vitamin A supplements to children each year.

Recent USAID-supported research has shown that giving vitamin A to infants at birth may yield a previously unknown reduction of approximately 20 percent or more in early infant mortality. USAID is supporting a large trial to confirm this finding in order to establish the evidence base required to advocate for newborn

Figure I.4. Key Events in the Diffusion of Vitamin A (VA)



vitamin A supplementation as a new means of substantially reducing early infant death from infection.

A recent WHO analysis indicated that the number of deaths of preschool-age children due to vitamin A deficiency has decreased from a mid-range estimate of 1.7 million per year in the late 1980s to approximately 700,000 per year, a decline that represents approximately 1 million lives saved per year.

USAID-funded cost-effectiveness research has established a strong case for making vitamin A supplementation the centerpiece of child survival activities. Recent research in three diverse countries (Nepal, Ghana, and Zambia) categorized costs as program-specific, personnel, and capital, and identified funding by source. These studies found that the average cost per death averted through vitamin A supplementation was about $65, which compared favorably with other child survival interventions such as vaccines.

USAID also supports its collaborating scientists in laying the "advocacy" groundwork in the antenatal care and obstetrics/gynecology communities to bring increased attention to maternal nutrition as a complement to emergency obstetric care practices in improving maternal health and survival.

Food Fortification

Funding since 1980 $25m

USAID Role in Research/Development/Application Life Cycle	
	**Assessment** Vitamin A deficiency, anemia prevalence surveys; technology assessment; consumption survey
	**Development** Organoleptic tests, stability and acceptability tests, technology trials, stability trials
	**Introduction** Prevalence surveys, food consumption surveys, acceptability tests, efficacy studies, cost-effectiveness studies, cost analyses
	**Coordination** World Food Program; United Nations Children's Fund; Pan American Health Organization; Micronutrient Initiative; Asian Development Bank. Table I.2 shows selected in-country partners among health, industry, and food ministries; standards institutes; associations of millers and other food producers; universities

USAID supported the assessment research on vitamin A deficiency and anemia prevalence and the development and introduction research necessary for large-scale food fortification programs. This research included organoleptic* tests, stability and acceptability tests, technology trials, and stability trials, and has resulted in food fortification programs that have made fortified sugar, cooking oils, and/or flours available to the majorities of the populations of Bangladesh, Nicaragua, Philippines, Zambia, Uganda, Eritrea, Morocco, West Bank/Gaza, and Ghana. Table I.2 on the next page provides the details of USAID-supported food fortification research in these countries, where USAID's partners have included the World Food Program; UNICEF; the Pan American Health Organization; the Micronutrient Initiative; health, industry, and food ministries; standards bureaus; national professional and trade associations; and local universities.

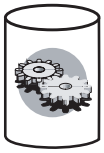
*Organoleptic, relating to perceptions by a sensory organ.

Table I.2. Role of USAID-Supported Research with Public-Private Partners in Food Fortification

Research	Country	Food Vehicle, Year	Fortificant	Partners	Estimated Population Covered
Efficacy study, organoleptic test, acceptability test, cost analysis	Bangladesh	Wheat flour, 2002	Vitamin A, iron, folate, B vitamins	Ministries of industries and food, World Food Program, oil producers, millers	85%
		Oil (proposed)	Vitamin A		65% (proposed)
Vitamin A deficiency and anemia prevalence survey	Nicaragua	Sugar, 2000	Vitamin A	Ministries of health and industries, national sugar association, wheat flour millers association, UNICEF, Pan American Health Organization, Micronutrient Initiative	100%
		Wheat flour, 1997	Iron, vitamin B		48%
Efficacy study, cost-effectiveness study, stability and acceptability tests	Philippines	Wheat flour, 2004	Iron, vitamin A	Bureau of Food and Drugs, Department of Health, UNICEF, Asian Development Bank, associations for each of the food vehicles	60%
		Sugar (proposed)	Vitamin A		–
		Oil, 2004	Vitamin A		35%
		Rice, 2004	Iron		13%
Prevalence survey, stability testing, utilization surveys	Zambia	Sugar, 1997	Vitamin A	Ministry of Health, UNICEF, Society for Family Health, Japanese embassy, Zambia Sugar PLC	70%
Feasibility assessment, prevalence survey, stability testing	Uganda	Oil, 2004	Vitamin A	Ministry of Health, Bureau of Standards, Makere University, Mukwano Oil, Unga 2000 (maize miller), Maganjo Millers	56%
		Maize flour, 2004	Vitamin A, B vitamins, iron, folic acid, zinc		0.1%
Technology assessment, consumption survey, cost analysis	Eritrea	Wheat flour (proposed)	Vitamin A, B vitamins, iron, folic acid	Ministries of health, industry, and trade; Eritrean Standards Institute; Keihbahri Millers; Red Sea Mills	50% (proposed)
Prevalence survey, technology trials, stability trials	Morocco	Oil, 2000	Vitamins A and D	Ministries of health and agriculture, official laboratories, national millers federation, oil industrialists association	70%
		Wheat flour, 2000	B vitamins, iron, folic acid		62%
Prevalence survey, assessment test development	West Bank/Gaza	Wheat flour (proposed)	Vitamins A and D, iron, B vitamins, folic acid	Palestinian Standards Institute, Ministry of Health, Berzeit University	57% (75% in Gaza) (proposed)
Prevalence survey, food consumption survey, acceptability test	Ghana	Oil, 1999	Iron, vitamin A	Ministries of trade and industry, food and drugs board, Ghana Health Service, Ghana Standards Board, Unilever, Irani Brothers, Takoradi Flour Mills, Ghana Agro Foods, University of Ghana Food Research Institute	40%
		Sugar (proposed)	Vitamin A		98% (proposed)
		Wheat flour (proposed)	Vitamin A, B vitamins, iron, folic acid, zinc		95% (proposed)

3. MICROBICIDES

Budget 2004	$21.8m
Funding Since 2001	$44.9m

USAID Role in Research/Development/Application Life Cycle	
	**Assessment** Studies of local HIV incidence among risk group, research capacity, and community awareness in preparation for clinical trials of new microbicides; future marketing potential; public health and programmatic impact; regulatory and policy environment and challenges for new product introduction
	**Development** Targeting the research and development of safe, effective, and acceptable microbicides with the appropriate cost and product characteristics for use in developing countries and in public sector programs
	**Introduction** Preliminary and formative studies to plan new product introduction and address issues related to regulatory policy and product approval in developing countries; manufacturing; distribution; marketing; provision through public sector programs, including integration with existing HIV and health programs; promoting correct and consistent use and acceptability
	**Coordination** National Institutes of Health; Centers for Disease Control and Prevention; Food and Drug Administration; World Health Organization; U.K. Department for International Development; Bill & Melinda Gates Foundation; International Working Group on Microbicides; Alliance for Microbicide Development; Global Campaign for Microbicides; CONRAD; Population Council; Family Health International; Program for Appropriate Technology in Health

A major problem in addressing the HIV/AIDS pandemic in developing countries is that current strategies for preventing HIV infection often are not available options for many women in these countries. To address this problem, USAID is engaged in research to develop female-controlled chemical barriers to HIV infection, i.e., microbicides. For more than a decade, USAID has had an effective and productive program to support the biomedical and behavioral research needed for the successful development of a microbicide. These efforts have yielded promising candidates that are entering the final stages of clinical testing in international trials for their safety, acceptability, and effectiveness in preventing or decreasing HIV transmission.

USAID has collaborated with NIH, CDC, and FDA to develop the U.S. Government's Strategic Plan for Microbicides. USAID has had a leading role and contributed to the following objectives of the Plan:

- *Preclinical development and evaluation of potential microbicide candidates* to support the discovery, characterization, and early-stage development of potential new active agents for use in microbicides
- *Formulation and delivery of potential microbicides* to develop and assess safe, acceptable, and effective formulations and modes of delivery for microbicides, applying knowledge from the chemical, pharmaceutical, physical, bioengineering, and social sciences
- *Clinical testing of microbicides* to assess the clinical safety, acceptability, and effectiveness of potential microbicides in reducing the transmission of HIV and sexually transmitted infections (STIs) (and in preventing pregnancy for products that are also contraceptive) in developing countries and the United States
- *Identification of behavioral factors and social science issues* to conduct behavioral and sociological research to enhance microbicide development and testing and to better understand factors that will affect future microbicide use and acceptability in developing countries
- *Provision of training and infrastructure* to establish, maintain, and strengthen the appropriate training and

Table I.3. USAID Cooperative Agreements for Microbicide Research and Development

USAID Cooperating Agency	FY 01 Obligations	FY 02 Obligations	FY 03 Obligations	FY 04 Obligations	FY 05 Obligations (planned)
Population Council	3,300 ($ thousands)	4,013 ($ thousands)	7,722 ($ thousands)	6,990 ($ thousands)	8,300 ($ thousands)
CONRAD Program	4,850	7,136	3,279	4,904	9,424
Family Health International	1,900	1,444	5,191	8,439	8,210
WHO	1,000	835	1,000	400	700
Global Campaign for Microbicides	0	947	529	221	430
Int'l. Partnership for Microbicides	0	0	0	0	1,984
CDC	450	250	0	698	583
PATH	0	375	170	81	129
EngenderHealth	500	0	0	0	0
Synergy Project	0	0	0	137	0
TOTAL	12,000	15,000	17,891	21,870	29,760

infrastructure needed to conduct microbicide research internationally and to accelerate future access to microbicides in diverse populations and settings

USAID's role in this U.S. government-wide effort is to focus research and development on safe, effective, and acceptable microbicides that have the appropriate cost and product characteristics for use in developing countries and in public sector programs.

This role is coordinated through extensive representation and collaboration in the efforts of the other U.S. government agencies in this field. This includes serving as a member of the Office of AIDS Research Microbicide Research Planning Committee for NIH, along with FDA, CDC, and other collaborators. USAID is also a very active member of the International Working Group on Microbicides, which was established by the Joint United Nations Program on HIV/AIDS and includes all of the relevant U.S. government agencies, multilateral and other donors, and international and national organizations that are supporting or conducting activities related to microbicide research and development. In addition, other U.S. government agencies and non-governmental partners also participate in the technical advisory committee meetings of the USAID cooperating agencies (CAs) in this field. This high level of coordination permits the full sharing of priorities and work plans, helps eliminate unnecessary duplication, and promotes sharing of resources and efficient collaboration for research. In particular, this collaborative approach has been very successful in coordinating algorithms for pre-clinical testing, prioritizing promising microbicide candidates, designing clinical testing protocols, building local research capacity, preparing communities for clinical trials, and learning from each other's experiences in these areas.

While part of a long-standing program, financial support for microbicide research and development through USAID increased significantly in fiscal year (FY) 2001, with $12 million provided by Congress explicitly for this purpose. This commitment has increased each year and is nearly $30 million in FY 2005. (see Table 1.3) USAID is implementing this program through eight grants and cooperative agreements in FY 2005 (see Table 1.3).

Table I.4. Phase III Microbicide Studies Supported by USAID

	Carraguard	Savvy (includes 2 studies)	Cellulose Sulfate	Cellulose Sulfate
# of Sites and Locations	3 in South Africa	2 in Ghana, 2 in Nigeria	2 in Nigeria	Benin, Burkina Fasa, Uganda, South Africa, 2 in India
Start of Screening & Enrollment	March 2004	March 2004	November 2004	June 2005
# of Volunteers to Be Screened	Approx 12,540	Approx 10,000	Approx 6,500	Approx 5,000
# Expected to Be HIV-Positive When Screened	Approx 5,016 (40%)	Approx 1,200 (12%)	Approx 975 (15%)	Approx 2,000 (40%)
# of Volunteers to Be Enrolled	6,300	4,284	2,160	2,574
Expected HIV Incidence Rate	3.5%	5%	5%	4%
# of HIV Seroconversions Expected During Study	450	132	66	66
Final Report Expected	October 2007	July 2007	August 2007	December 2008
USAID Partner Conducting Trial	Population Council	Family Health International	Family Health International	CONRAD Program

These cooperative agreements use subawards as needed to accomplish their research objectives.

USAID's role in microbicide research and development extends beyond financial support to include technical leadership, both among U.S. government agencies and throughout the international microbicide and HIV prevention field. USAID has had a critical and essential role in shaping the strategic direction of research in this field as well as in leveraging and coordinating the intellectual, proprietary, and financial capital of a host of contributors, including private foundations (especially the Bill & Melinda Gates Foundation) and commercial parties.

The FY 2004 initiation of large-scale clinical efficacy trials for USAID-sponsored microbicide candidates confirms the success of this USAID research effort. In collaboration with other agencies and donors, USAID is supporting the testing of Carraguard™, Cellulose Sulfate, and Savvy™ brand microbicides in thousands of volunteers, as required for international phase III studies. (see Table 1.4)

These large clinical studies are required by the FDA to determine if these products successfully can prevent or reduce the sexual transmission of HIV. They will be the first trials in humans to evaluate the effectiveness of this new prevention technology and will have a critical role in demonstrating that a microbicide can be effective in making a significant contribution to preventing HIV infection.

Research and development of other product leads have also been supported partially by USAID and will undergo advanced testing with other sources of primary funding. Buffergel™, for example, has just begun phase III advanced testing by the HIV Prevention Trials Network funded by NIH. All of

these current products are formulated as gels that are applied vaginally before intercourse. The safety of each has been tested extensively in phase II clinical trials.

The largest part of the USAID microbicide research and development budget (over 74 percent in FY 2004) is being used to support these essential phase III clinical studies. The remaining funds are being used to develop capacity at sites for future clinical studies, advance research on selected second-generation microbicide leads, and address limited policy and logistical issues that will be critical to successfully introducing microbicides in developing countries when available.

When the testing of a safe, effective, acceptable and affordable microbicide is completed, it will be introduced and made readily available in developing countries as soon as possible. With its extensive experience in distribution, logistics management, service delivery, provider training, and social marketing, USAID and its partners will be well positioned to introduce this new prevention technology and support its appropriate and effective use in the fight against HIV/AIDS in developing countries.

4. CONTRACEPTIVE TECHNOLOGIES

Budget 2004 $8.8m*

*Contraceptive R&D

USAID Role in Research/Development/Application Life Cycle	
	**Assessment** Knowledge and understanding of effectiveness, long-term safety, and acceptability of contraceptive methods
	**Development** Improving existing and developing new contraceptive technologies; identifying and testing innovative approaches to improving effectiveness and efficiency of family planning (and related reproductive health) service delivery
	**Introduction** Expanded variety of effective contraceptive methods available in USAID-supported family planning programs worldwide
	**Coordination** Eastern Virginia Medical School (CONRAD Program); Family Health International (Contraceptive Technology Research Program); the Population Council (Product Development Agreement); Georgetown University (Institute for Reproductive Health); Program for Appropriate Technology in Health (HealthTech IV Program); World Health Organization (Reproductive Health and Research Department); Centers for Disease Control and Prevention (Division of Reproductive Health); National Institute of Child Health and Human Development; Food and Drug Administration; United Nations Population Fund; Department for International Development (U.K); Bill & Melinda Gates Foundation; Hewlett Packard, Rockefeller, and Buffet foundations; Pfizer Inc.; Wyeth; Ortho-McNeil Pharmaceutical; Schering AG; Organon

USAID funds a wide range of research (including biomedical, operations, social science, demographic, and policy-related research) and relevant technical assistance that has a direct effect on increasing contraceptive use, reducing total fertility rates, and improving maternal and child health. USAID's research objectives in the areas of contraceptive development and improving service delivery are to:

- Develop and introduce improved and new contraceptive technologies, including methods that also reduce the risk of transmission of HIV and other STIs
- Understand issues of and increase knowledge about contraceptive effectiveness, long-term safety, and acceptability
- Identify and test innovative approaches to improving the effectiveness and efficiency of delivering family planning and related reproductive health services

To achieve these objectives, USAID's contraceptive research portfolio includes the following:

- Developing and implementing preclinical, clinical, and acceptability studies on a wide range of methods, including barrier methods such as male and female condoms, diaphragms and cervical caps, and some microbicides for dual protection from unintended pregnancy and HIV/STIs; long-acting hormonal methods such as implants, injectables, and vaginal rings; improved delivery technologies such as safer injection systems for injectable contraceptives; new methods for men such as long-acting injectable or implantable hormonal methods; nonsurgical and possibly reversible methods of male and female sterilization; and natural methods of family planning, such as the new Standard Days Method and the TwoDay Method
- Assessing the effectiveness, safety, and long-term risks and benefits of current and new contraceptive methods through epidemiological studies and the acceptability of these methods to clients and providers through introduction studies
- Producing and disseminating state-of-the-art information and guidelines regarding current and new

technologies to policymakers, program managers, providers, and clients

- Analyzing service delivery capacity to add new technologies

Support for Contraceptive Research and Development: Support for USAID contraceptive research and development has been relatively constant over the past 15 years and is a critical component of USAID's ability to provide improved and new methods, gain better understandings of current methods, and increase the overall use of family planning. An expanded variety of methods gives clients more choices appropriate to needs and lifestyles and thus ensures more effective use.

USAID's contraceptive research and development program strengthens family planning services by helping to provide methods that are:

- More effective in preventing unintended pregnancy
- More acceptable and therefore more likely to be used correctly and for longer duration
- Safer to use with fewer side effects
- Easier to provide and more affordable even in low-resource settings
- In some cases, also protective against STIs, including HIV

The contraceptive research and development program is fully integrated within USAID's comprehensive family planning program and is thus driven by the needs of family planning providers in developing countries and the "end users/customers." This integration is the key to USAID's success and its unique contribution as the primary donor agency concerned with methods appropriate for use in developing-country settings.

Coordination: USAID has been highly successful in coordinating its contraceptive research and development program with other federal agencies, intergovernmental agencies and multilateral donors, other bilateral donors, private foundations, and pharmaceutical companies. This type of important interagency coordination is supported by the strong collaboration among USAID-supported CAs involved in contraceptive research and development. Coordination across the various organizations and agencies is accomplished in many ways, including individual contacts and networking by USAID staff; participation in advisory group meetings; frequent communication by phone and e-mail between agencies and partners; and the sharing of proposals, protocols, and other working documents. Each USAID CA has a technical advisory committee consisting of outside technical experts and representatives from collaborative CAs, other U.S. government agencies (NIH, CDC, and FDA), and foundations. In many cases there is joint programming between USAID CAs and between USAID and other donors. This level of coordination has eliminated unnecessary duplication of effort and has facilitated cost-sharing with other donors. A testimony to the vibrancy of USAID's efforts in contraceptive research and development is the transfer of funding from NIH and CDC to USAID through interagency agreements to support the USAID contraceptive research and development program.

Except for the United Kingdom's Medical Research Council and the Indian Council for Medical Research, other national institutions do not provide much (if any) support for applied research in this field. NIH primarily supports basic research in reproductive sciences, and the relatively limited funds it spends on contraceptive development are focused on methods for U.S. consumers. The WHO Human Reproduction Program, which used to be a major player in contraceptive research and development, has greatly scaled back its work in this area over the past several years due to limited resources and a greater focus on longer-term epidemiological studies of current methods. Clearly, USAID has become the lead donor agency supporting research on family planning methods for developing countries.

With few exceptions, private sector drug companies are not prepared to pursue contraceptive development, particularly of methods appropriate for use in low-resource settings, because of issues related to product liability and the limited profit potential. The majority of the multinational pharmaceutical industry's contraceptive

Table I.5. Contraceptive Products Under Development and/or on the Market

Product	Cooperating Agency Partner(s)	Commercial Partner(s)
NORPLANT Implant System	Population Council	Schering OY
Jadelle Implant System	Population Council	Schering OY
Mirena IUD	Population Council	Schering OY
Progesterone Vaginal Contraceptive Ring	Population Council; CONRAD	Silesia (Chile) [available in Chile only]
Reality Female Condom	CONRAD; FHI	Female Health Company
Filshie Clip for Female (Tubal) Sterilization	FHI	Femcare, Ltd. (UK)
Tactylon Condom	FHI	Sensicon Corp.
eZ-on Condom	FHI	Mayer Laboratories
Lea's Shield Cervical Cap	CONRAD; FHI	Yama, Inc. (sold via the Internet)
Femcap Cervical Cap	CONRAD; FHI	Femcap, Inc. (sold via the Internet)
Reddy Female Condom	CONRAD; FHI	Medtech Products, Ltd. (India)
Standard Days Method (Cycle Beads)	Georgetown University	Cycle Technologies (Hong Kong)
Depo-Provera in Uniject	PATH	Pfizer; Becton, Dickinson
Woman's Condom	PATH; CONRAD	
Nesterone-EE Vaginal Ring	Population Council	

research and development effort focuses on improvements in, or new ways of presenting, oral contraceptives, mainly for marketing to customers. In the past 10 years, the pharmaceutical industry has introduced four new methods – a one-week contraceptive patch, a one-month vaginal ring, a three-year single rod implant, and a five-year hormone-releasing intrauterine device (IUD) – all of which use the standard hormones found in oral contraceptives and none of which are affordable in low-resource settings.

While aimed primarily at methods for developing countries, USAID research has had direct and important benefits for American women and men, including the availability of the female condom, improved methods of sterilization for men and women, and the extended 10-year use-life of the world's most popular IUD, the CuT-380A.

Impact: USAID-supported research has resulted in the availability of a wider variety of new contraceptives and improvements in the understanding of existing technology. (see Table 1.5) Advances in these areas include:

- Long-acting implantable contraceptive systems such as NORPLANT and Jadelle
- Female barrier methods such as the Reality female condom, Lea's Contraceptive Shield, and FemCap
- Improved knowledge, including better understanding of which vasectomy techniques for male sterilization have the highest effectiveness; recognition that low-

dose oral contraceptives are as effective and safer than higher-dose pills; and recognition that IUDs can be used safely by young women without affecting their fertility and are appropriate for use even in settings with high rates of STIs and HIV and by women who have HIV

Research supported by USAID on natural family planning has led to the development of two new methods, the Standard Days Method and the TwoDay Method, both of which have been shown to be very effective when used correctly. Finally, operations research has made dramatic improvements in how clients are served and thereby increased the acceptance and use of family planning.

Research has shown that improved provider and user knowledge about family planning methods, and an increase in the number of methods available, result in more people using family planning effectively. When more people use family planning, there are fewer unintended pregnancies, fewer abortions, and reductions in maternal mortality. Thus, USAID's long-term investments in contraceptive research and service delivery improvement significantly contribute to the Agency's aims of reducing unintended pregnancies and improving maternal and child health and survival.

Case Study – Depo-Provera in Uniject:
USAID is working to maximize the safety of injections and minimize the likelihood of transmitting bloodborne infections, including HIV and other STIs, during injection procedures. While injectable female contraception represents only a minute amount of the total number of injections administered annually around the world, USAID showed leadership in the donor community by bundling Depo-Provera, the most popular three-month injectable contraceptive, with auto-disable (AD) syringes and safe disposal boxes. Other donors that supply contraceptive commodities, such as the United Nations Population Fund and the International Planned Parenthood Federation, also have switched to providing AD syringes with their shipments of Depo-Provera.

In a move to further increase injection safety and safe medical waste disposal while further expanding the use of Depo-Provera, USAID has developed a public-private partnership with the Pfizer pharmaceutical company (Depo-Povera's manufacturer); the USAID-supported PATH project, which developed the Uniject injection device (a proprietary prefilled AD device designed to prevent reuse); and Becton, Dickinson and Company, the world's largest syringe manufacturer and licensee of Uniject. USAID is providing leadership to the overall program and will procure and distribute Depo-Provera in Uniject once the new delivery system is ready for roll-out. At the time of this report, it appears that the parties will be successful in all aspects of this breakthrough work.

5. MALARIA

Budget 2004	$10.4m
Budget 2003	$8.7m
Budget 2002	$8.1m

USAID Role in Research/Development/Application Life Cycle	
	**Assessment** Documenting feasibility, acceptability, safety, and impact of malaria prevention and treatment technologies; research to monitor spread of drug-resistant malaria
	**Development** New drugs for treating severe and complicated malaria and uncomplicated malaria; new technologies for improved home management of uncomplicated malaria; new technologies for re-treating mosquito nets with insecticides
	**Introduction** Support for adoption of new artemisinin-based combination treatment therapies in sub-Saharan Africa and South America; studies of consumer demand for and practices using insecticide-treated nets in Africa
	**Coordination** World Health Organization; Centers for Disease Control and Prevention; Medicines for Malaria Venture; Kenan Institute of Asia; U.S. Pharmacopeia Drug Quality and Information Project Project; Italian government; U.K. Department for International Development; Swiss Tropical Institute; FCB Advertiser Group Africa; Siam Dutch Company

USAID-supported non-vaccine-related malaria research is targeted at developing high-priority tools, such as insecticide-treated mosquito nets (ITNs) and new and improved drugs, and operations research to improve the delivery of current prevention and treatment options.

Insecticide-Treated Mosquito Nets: ITN use for malaria prevention is now scaling up throughout Africa. USAID-supported research has been a large contributor to the evidence base supporting this scale-up:

- Throughout the 1990s, USAID supported large-scale efficiency trials of ITNs across Africa. These trials provided definitive data on the highly effective impact of ITNs for preventing malaria among the most vulnerable populations of women and children. Their impact included decreases in both morbidity and mortality, with reductions in clinical cases of malaria of 40 percent to 50 percent and in under-5 mortality from all causes of about 20 percent. USAID coordinated its support for these trials with funds from the Italian government, the U.K. Department for International Development, the Swiss Tropical Institute, and WHO. USAID also provided funds directly to CDC to carry out a large-scale trial in western Kenya.
- In 2004, USAID supported the development research for a long-lasting net re-treatment using a new insecticide with built-in chemical linkers. This technology extends the ITN's "life" from six months to five years. The research to develop a large-scale industrial process for this technology was coordinated with the Siam Dutch Company, a private manufacturer in Thailand.
- USAID supports ongoing ITN introduction research, including studies of consumer demand and practices in Africa. This research is carried out in coordination with FCB Advertiser and Group Africa, both of South Africa.

New Drug Development: As increasing drug resistance makes many of the available drugs ineffective, research to develop new malaria drugs is important. In the 1990s, USAID supported early clinical trials of the efficacy and safety of artemisinin-based combination therapy (ACT) in children in Africa. Now recommended by WHO, ACT is the best malaria treatment currently available and is being rolled out throughout Africa. It is expensive, however, and eventually will encounter drug resistance.

- *New drugs for severe and complicated malaria:* With USAID support, WHO's Special Program for

Research and Training in Tropical Diseases (TDR) is developing a rectal formulation of artesunate, a semisynthetic derivative of artemisinin, for the purpose of reducing the risk of a fatal outcome in patients (mainly infants and children) with life-threatening malaria. The purpose of this development has been to provide a safe and effective emergency substitute for injectable therapy for patients in malaria-endemic areas who do not have immediate access to injectable antimalarial treatment and cannot take drugs by mouth due to the severity of the disease. Ongoing activities address remaining regulatory questions in order to register rectal artesunate in the United States and include efficacy and safety trials to establish clinical benefit and drug safety in use conditions.

- *New drugs for uncomplicated malaria:* In 2004, USAID established a multiyear grant to the Medicines for Malaria Venture (MMV), a public-private partnership that manages a research and development portfolio of 22 drugs. The MMV portfolio emphasizes developing drugs that are effective against drug-resistant strains of *P. falciparum*; improve patient compliance with therapeutic regimens of three days or less; have a low propensity for drug resistance; are safe in young children and pregnant women; and have potential for use in intermittent treatment during pregnancy. Two of the most attractive products are a pediatric formulation of artemether-lumefantrine (Coartem) and a less expensive synthetic peroxide drug similar to artemisinin. USAID funding represents about 10 percent of MMV's total budget.

Operations Research: USAID also invests in operations research to improve or test new approaches or to resolve key implementation questions.

- *Improved management of uncomplicated malaria:* USAID supports TDR to conduct field research to identify the factors determining the successful deployment of home management of malaria with ACT; to understand the factors that impede deployment of home-based management of malaria; and to assess the impact of such programs. Special emphasis is being placed on:
  - Documenting the feasibility, acceptability, and safety of new and more effective antimalarial drugs in the home management of malaria
  - Improving unit dose blister packaging; appropriate labeling of drugs; and information, education, and communication to increase provider and patient compliance
  - Developing innovative procurement systems for prepackaged drugs at the community level, in particular through public-private collaboration, in order to achieve maximum coverage
  - Strengthening the capacity for social science research as a fundamental component of implementation research and home management of malaria
  - Developing an intervention for home and community management of malaria and pneumonia that is safe, feasible, acceptable, and achieves high coverage and adherence
- *Assessing the impact of ACT in Africa:* Since 2000, USAID has supported CDC in evaluating the use of ACT and the development of drug resistance in *P. falciparum* malaria in a high-transmission area of sub-Saharan Africa. This evaluation includes components of population genetics, molecular biology, sociobehavioral science, policy analysis, economic analysis, and public health impact. The evaluation is taking place in four districts in coastal and central Tanzania and benefits from existing infrastructure, such as a demographic surveillance system, geographic information system capabilities, and well-developed laboratory capacity at the Ifakara Health Research and Development Centre, the primary in-country collaborating institution. Expected outcomes include the first (and likely only) population-based data on the effect of ACT use at program scale on inhibition of drug resistance and health outcomes (including mortality); on the costs and cost-effectiveness of ACT-based policies; and on the acceptance and use of ACT by health care providers and patients. This project already has provided valuable experience on drug policy and ACT implementation that has influenced the development

and roll-out of new treatment policies in Zanzibar, Burundi, the Democratic Republic of the Congo, and countries in South America.

- *The emergence and spread of drug resistance:* Increased exposure of disease-causing pathogens to sublethal doses of antimicrobial drugs has resulted in increasing rates of drug-resistant malaria, tuberculosis, and HIV/AIDS. To better understand the factors that underlie the emergence and spread of drug resistance for malaria, USAID has been supporting a comprehensive research program in the Mekong Basin countries of Southeast Asia. The program is focusing particularly on:
  - Monitoring the efficacy of recommended antimalarial medicines in South and Southeast Asia to determine if drug policies are appropriate or need to be updated
  - Studying care-seeking behaviors and antimalarial drug use practices of prescribers and consumers in Cambodia and Thailand to identify barriers to appropriate use of recommended therapy
  - Monitoring the quality of antimicrobial medicines to treat malaria (as well as TB, HIV/AIDS, and childhood illnesses) available in the public and private health sectors in South and Southeast Asia to obtain better information for raising awareness among policymakers, other donors, prescribers, and consumers, and for developing and applying interventions to improve the quality of medicines available in Asia
  - Comparison of indoor residual spraying and insecticide treated nets

In late 2004, USAID commissioned a review by Brian Sharp, Medical Research Council, Durban, South Africa, and Christian Lengeler, Swiss Tropical Institute, Basel, Switzerland to compare indoor residual spraying (IRS) and insecticide treated nets (ITNs) across a range of malaria transmission settings in sub-Saharan Africa in terms of cost-effectiveness, impact on health measures, and operational constraints. This study includes: a systematic review of the health impact of IRS for malaria (which already exists for ITNs); a cost-effec-

Table I.6. Primary Malaria Research Fund Recipients*

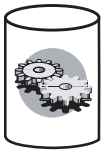
Malaria Research Fund Recipients	FY 2002	FY 2003	FY 2004
Center for Disease Control	$230,000	$1,330,000	$1,530,000
Malaria Vaccine Initiative	N/A	N/A	$1,500,000
Maxygen	$1,300,000	$1,200,795	$1,208,948
Medicines for Malaria Venture	N/A	N/A	$1,500,000
Navy Medical Research Center	$1,000,000	$1,000,000	$1,000,000
RPM-Plus			$200,000
Walter Reed Army Medical Research Center	$2,070,000	$2,094,205	$1,811,052
World Health Organization	$1,689,000	$1,315,000	$457,000
Total	**$6,289,000**	**$6,940,000**	**$9,207,000**

*USAID/Washington funding only

tiveness assessment of both IRS and ITNs in large-scale programs in sub-Saharan Africa; and a comparative assessment of operational and structural issues in deploying IRS and ITNs in different epidemiological settings in Africa. The report is expected in early 2006, and will provide clear, evidence-based guidance to National Malaria Control Programs and USAID missions on key factors to consider when selecting vector control interventions in specific settings to ensure maximum public health effectiveness for money spent.

6. TUBERCULOSIS

Budget 2004	$7.8m
Budget 2003	$6.2m
Budget 2002	$6.9m

USAID Role in Research/Development/Application Life Cycle	
	**Development** New diagnostics, drug regimens, and approaches appropriate for use in low-resource countries to improve DOTS (directly observed treatment, short course) TB control programs
	**Introduction** Support for expanded and more effective DOTS programs in USAID-assisted developing countries worldwide
	**Coordination** World Health Organization; Centers for Disease Control and Prevention; TB Diagnostics Initiative at the Special Program for Research and Training in Tropical Diseases (a World Health Organization/United Nations Children's Fund/World Bank program); Johns Hopkins University; University of Alabama, Birmingham; International Union Against Tuberculosis and Lung Disease; Global Alliance for TB Drug Development, NIH/Fogerty

USAID's TB research portfolio focuses on the development, evaluation, and introduction of new and improved tools and approaches that are appropriate for use in low-resource countries.

New and Improved Drugs and Drug Regimens: USAID supports the development of new drug treatment regimens and new drugs that can shorten and simplify treatment, a high priority for the global TB community.

The first of two studies supported by USAID compared two drug regimens in the continuation phase of treatment. The results of this study, conducted by the International Union Against Tuberculosis and Lung Disease (the Union), were published in *The Lancet* in October 2004 and confirmed that a six-month course of treatment with a specific set of drugs was more effective than an alternate eight-month course with other drugs. These results are now included in the *International Standards of Care for TB Treatment*. The second multicenter trial is intended to evaluate the efficacy, acceptability, and toxicity of a four-drug fixed-dose compound in the initial intensive phase of treatment chemotherapy. USAID also supports a phase III trial through the TDR to evaluate a four-month fixed-dose combination product containing gatifloxacin.

In 2004, USAID also entered into a new agreement with the Global Alliance for TB Drug Development.

New Diagnostics: USAID supports efforts to improve microscopy methods and accelerate the development of new point-of-care TB diagnostic technologies to diagnose active cases of TB. USAID also supports efforts to develop more appropriate and rapid methods for culture and susceptibility testing of mycobacterium TB that have direct relevance for the quality of treatment of TB patients.

USAID also supports the development of a TB specimen bank to increase access to reference materials to aid in the development of new diagnostics; the strengthening of clinical trial site preparedness; the development of regulatory quality standards for diagnostics trials; the evaluation of a new rapid and inexpensive diagnostic tool called TK Medium; and a laboratory-based evaluation of new point-of-care diagnostics.

New Approaches to Improving DOTS: The growing HIV/AIDS epidemic, human resource constraints, and multidrug resistance have made improvements to the DOTS (directly observed treatment, short course) strategy critically important. The role of USAID in the global research agenda addressing these issues includes:

- *Clinical trials to test treatment approaches for TB-HIV/AIDS co-infection:* These trials are examining

the efficacy, safety, and feasibility of concomitant use of TB and HIV drugs in co-infected patients.

- *Studies on TB management:* Areas and types of studies include:
  - Cost-effectiveness of methods of TB drug-sensitivity testing
  - Prospective study of treatment relapse of new sputum smear-positive TB patients treated with the recommended category 1 treatment regimen
  - Role of incentives in improving DOTS program performance
  - Surveys of resistance to first-line anti-TB drugs
  - Archive of isolates for drug sensitivity and DNA fingerprinting
  - Evaluation of methods to control transmission of MDR-TB in health facilities and approaches to treat multiple drug resistant TB
  - Evaluation of the development of new drug resistance in DOTS Plus pilot projects
  - Testing of model approaches to involve private sector providers in DOTS

Operations Research to Improve Care of Persons Infected with TB and HIV: Operations research topics have included:

- Use of cotrimoxazole preventive therapy and chest x-ray screening for TB in HIV-positive persons
- Impact of antiretroviral treatment on TB epidemiology
- Use of quantiferon to detect latent TB infection in HIV-positive persons
- Testing of model primary health care service delivery approaches for care and treatment of persons co-infected with HIV/AIDS and TB
- Active TB case finding in HIV voluntary counseling and testing (VCT) centers

USAID's early support of the "ProTest" approaches to TB-HIV co-infection resulted in workable models for addressing TB-HIV co-infection that are now being scaled up in multiple countries in Africa and are also included in the WHO Stop TB Partnership guidance on TB-HIV. USAID also provides support to Johns Hopkins University for an operations research study in South Africa to measure the effectiveness of an interven-

Table I.7. Primary Tuberculosis Research Fund Recipients

Tuberculosis Research Fund Recipients	FY 2002	FY 2003	FY 2004
Center for Disease Control	$200,000	$175,000	$295,000
International Union Against Tuberculosis and Lung Disease (IUATLD)*	$650,000	$2,300,000	$2,600,000
TB Drug Alliance	N/A	N/A	$600,000
Gorgas/UAB/JHU	$2,350,000	$1,000,000	$1,500,000
World Health Organization	$375,000	$885,000	$910,000
TB Research Center Chennai, India	$1,250,000	$1,400,000	$1,382,500
Total	**$4,825,000**	**$5,760,000**	**$7287,500**

*In 2002 USAID's funding of the IUATLD clinical trials was channeled through USAID'S agreement with the TB Coalition for Technical Assistance.

tion aimed at increasing the uptake of HIV counseling by TB patients as they register and start taking TB medication. In addition, USAID is supporting the University of Alabama, Birmingham, in implementing an operations research study in Cambodia aimed at increasing active TB case finding by utilizing VCT services as a key starting point for reducing TB morbidity and HIV-associated mortality.

Section II

Fast Facts and Trends, 2002-2004

- USAID invests 6 to 7 percent of its total health-related budget in research and development. This percentage represented approximately $112 million in 2002, $123 million in 2003, and $155 million in 2004 (Table II.1).
- The proportion of funding obligated to research ranges from around 5 percent for child survival and maternal health (CS/MH)*, to between 5 and 10 percent for HIV/AIDS and family planning and reproductive health (FP/RH), to between 10 and 15 percent for infectious diseases (ID) (Table II.1).
- From 2002 to 2004, the total amount of funding for research grew from $112 million to $155 million. The health issue or disease with the largest single share of that funding for all three years was HIV/AIDS (37%, 37%, 46%), followed in descending order by Family Planning/Reproductive Health (29%, 32%, 24), Child Survival, Maternal Health, including Polio and Micronutrients (14%, 15%, 14%), Malaria (7%, 7%, 7%), TB (6%, 5%, 5%), and AMR, Surveillance and Other ID (7%, 4%, 3%). (Figures 11.3-11.5).
- While USAID/Washington centrally manages the largest number of research activities, the proportion of research managed by USAID missions increased from 15 percent of activities in 2002 to 21 percent in 2004 (Figure II.7).
- Introduction research is the largest share of research activities (45 percent); assessment and development research are at about the same level, around 27 to 28 percent (Figure II.8).
- USAID missions originate the majority of assessment research activities (60 percent missions, 40 percent USAID/Washington) (Figure II.8).
- USAID/Washington originates the majority of development research activities (75 percent USAID/Washington, 25 percent USAID missions) and introduction research activities (65 percent USAID/Washington, 35 percent USAID missions) (Figure II.8).
- The recipient of USAID's research investments include collaborating agencies and partners such as grantees and contractors; universities; NGOs/PVOs; host governments; the Centers for Disease Control and Prevention; the National Institutes of Health; and the Department of Defense (Table II.3).

* This percentage is lowered by the GAVI funds included in this overall account (between $55 and $65 million)

Table II.1. Amount/Percent of Health or Disease Area Funding Used for Research, FY 2002-2004

Health or Disease Area	2002		2003		2004	
	$ Mil	Percent of Total Funding	$ Mil	Percent of Total Funding	$ Mil	Percent of Total Funding
HIV/AIDS	$41	8%	$46	7%	$72	6%
Family Planning/Reproductive Health	$33	7%	$40	9%	$38	9%
Infectious Diseases (inclusive of AMR/other ID, malaria, TB)	$23	12%	$20	11%	$23	11%
Child Survival/Maternal Health (inclusive of polio and micronutrients)	$16	4%	$18	5%	$22	5%
Vulnerable Children	$0	0.06%	$ -	0%	$1	2%
Total Obligation on Research	**$112**	**7%**	**$123**	**6%**	**$155**	**7%**

Table II.2. Distribution of Total USAID Health-Related Research Funding by Each Major Health or Disease Area

Health or Disease Area	2002	2003	2004
HIV/AIDS	37%	37%	46%
Family Planning/Reproductive Health	29%	32%	24%
Infectious Diseases (inclusive of AMR/other ID, malaria, TB)	20%	16%	15%
Child Survival/Maternal Health (inclusive of polio and micronutrients)	14%	15%	14%
Vulnerable Children	0.02%	0%	0%
Total	**100%**	**100%**	**100%**

Figure II.1 Total Research Funding by Health Issue or Disease, FY 2002-2004

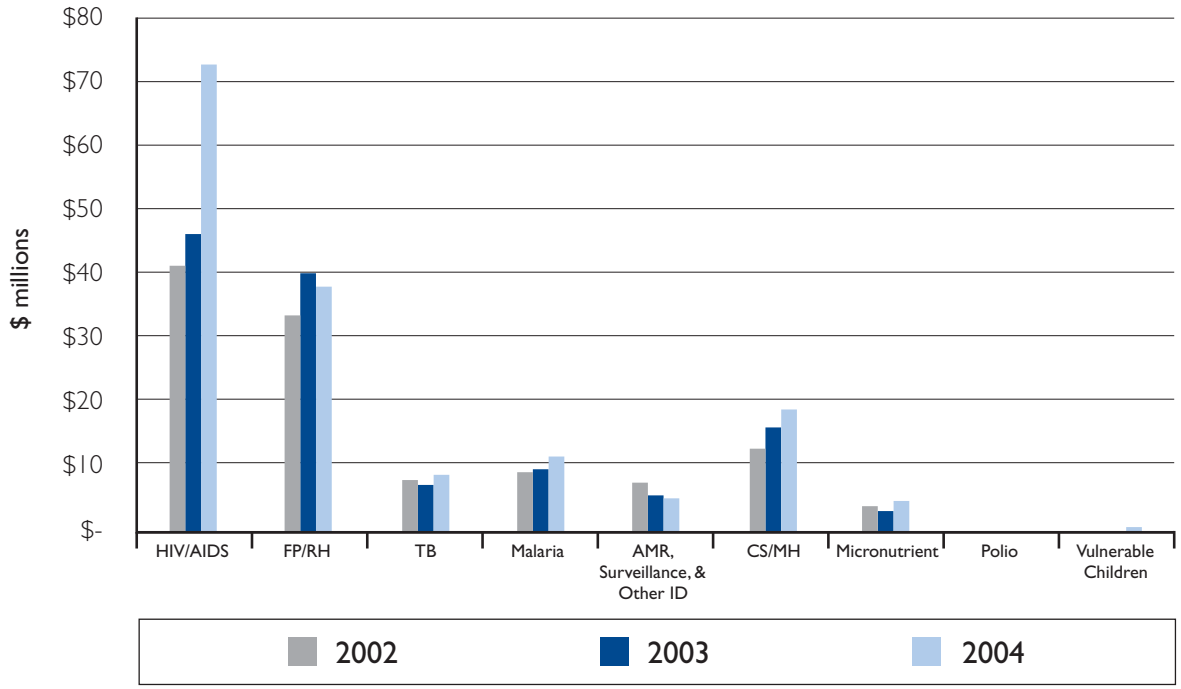


Figure II.2 Research Portion of Total Funding by Health Issue or Disease, FY 2002-2004

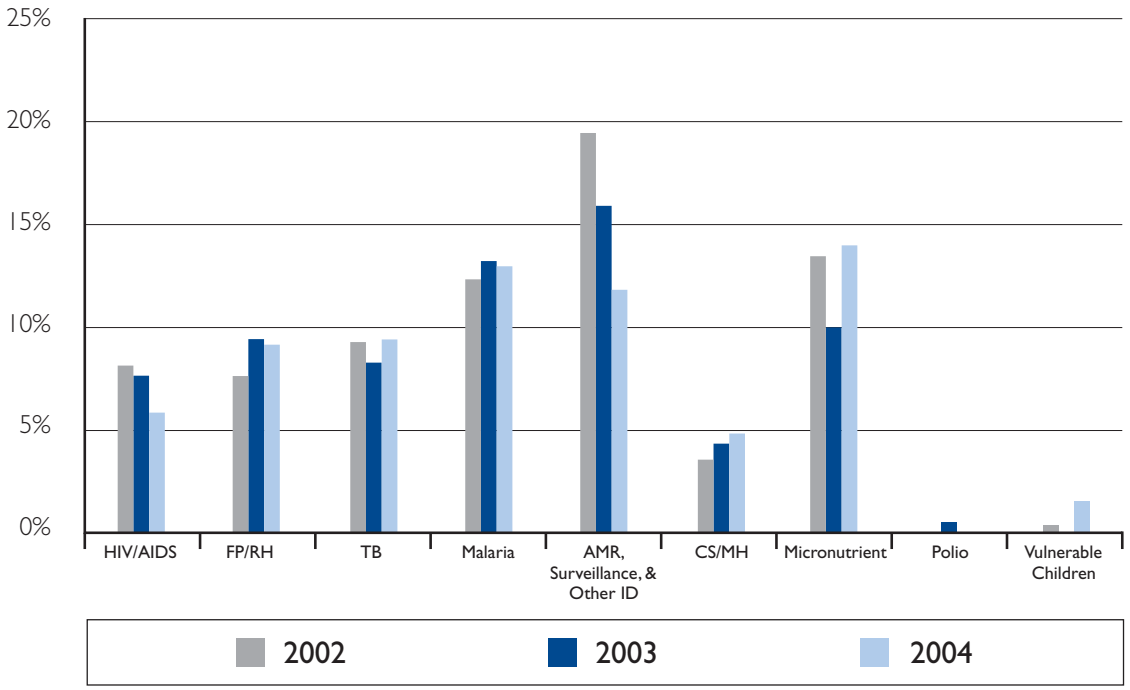
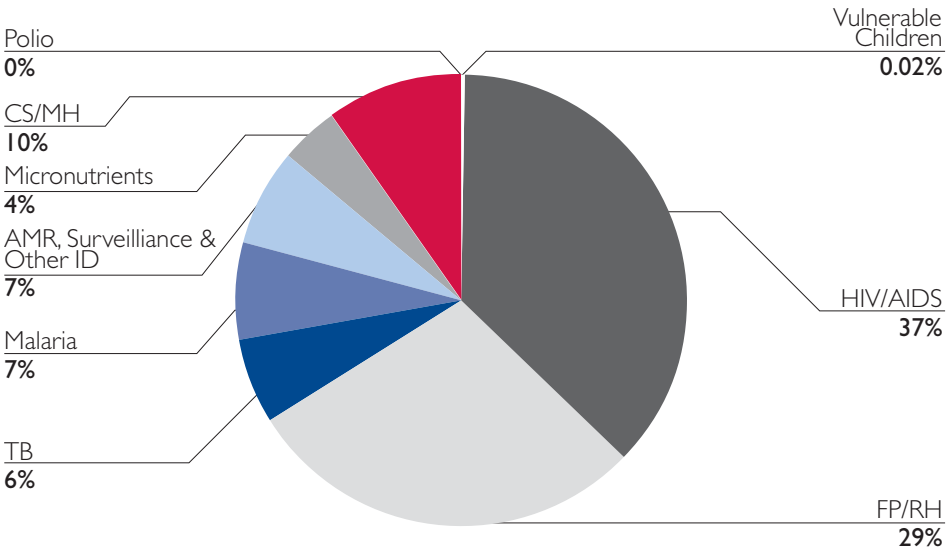
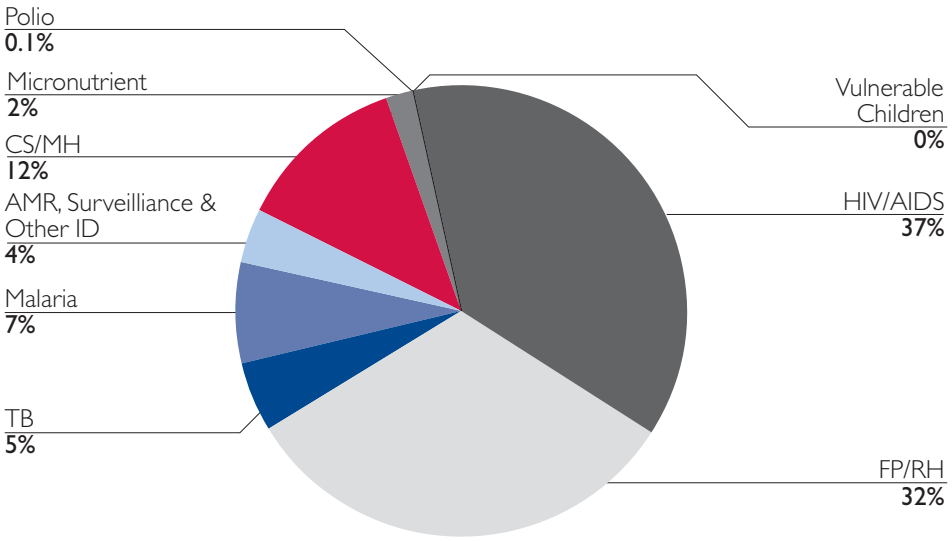


Figure II.3 Distribution of Research Funding by Health Issue or Disease, FY 2002



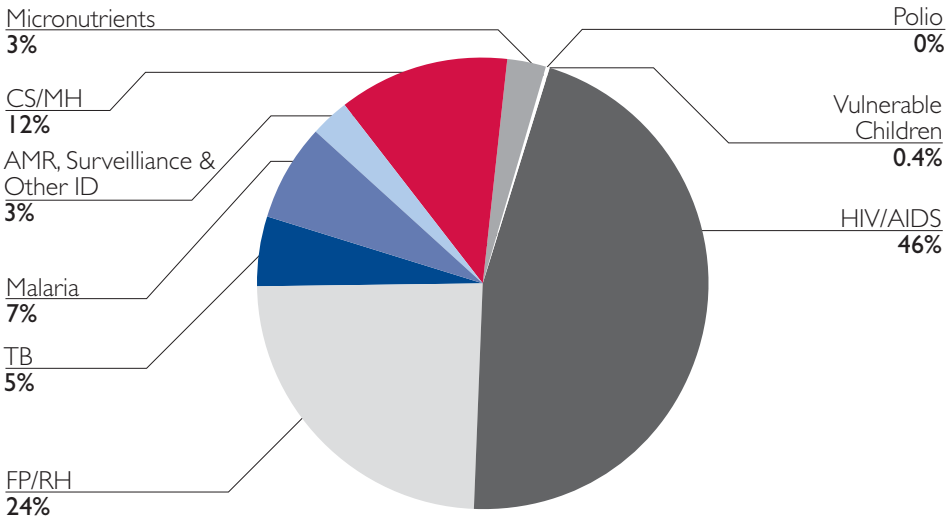
Total = $112M

Figure II.4 Distribution of Research Funding by Health Issue or Disease, FY 2003



Total = $123M

Figure II.5 Distribution of Research Funding by Health Issue or Disease, FY 2004



Total = $155M

Figure II.6 Research Funding as Part of Total Funding for Health, FY 2002-2004

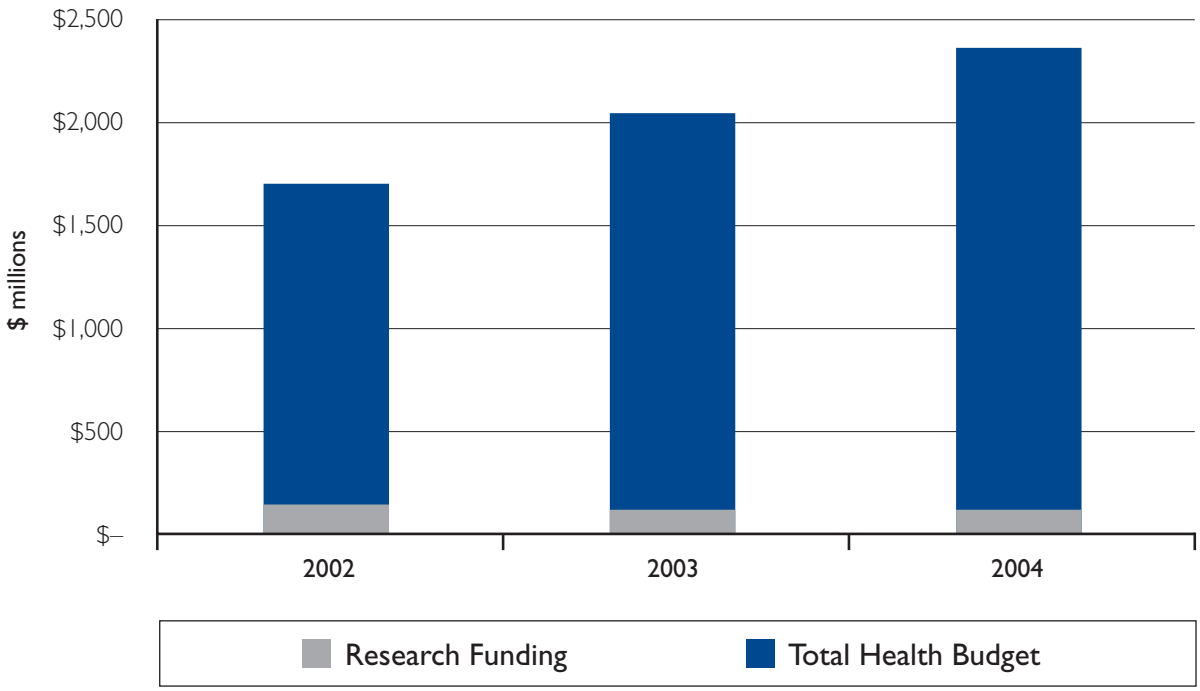


Figure II.7 Research Funding by Origin, FY 2002-2004

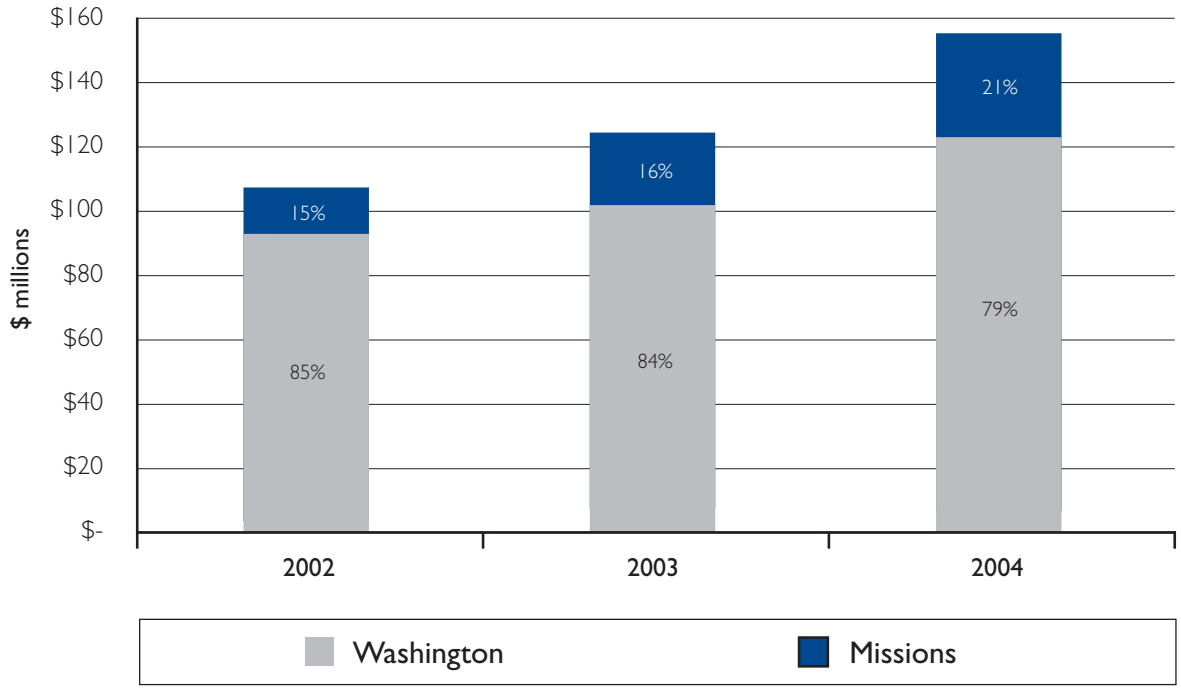


Figure II.8 Stage of Research Activity, FY 2002-2004 (n=1321)

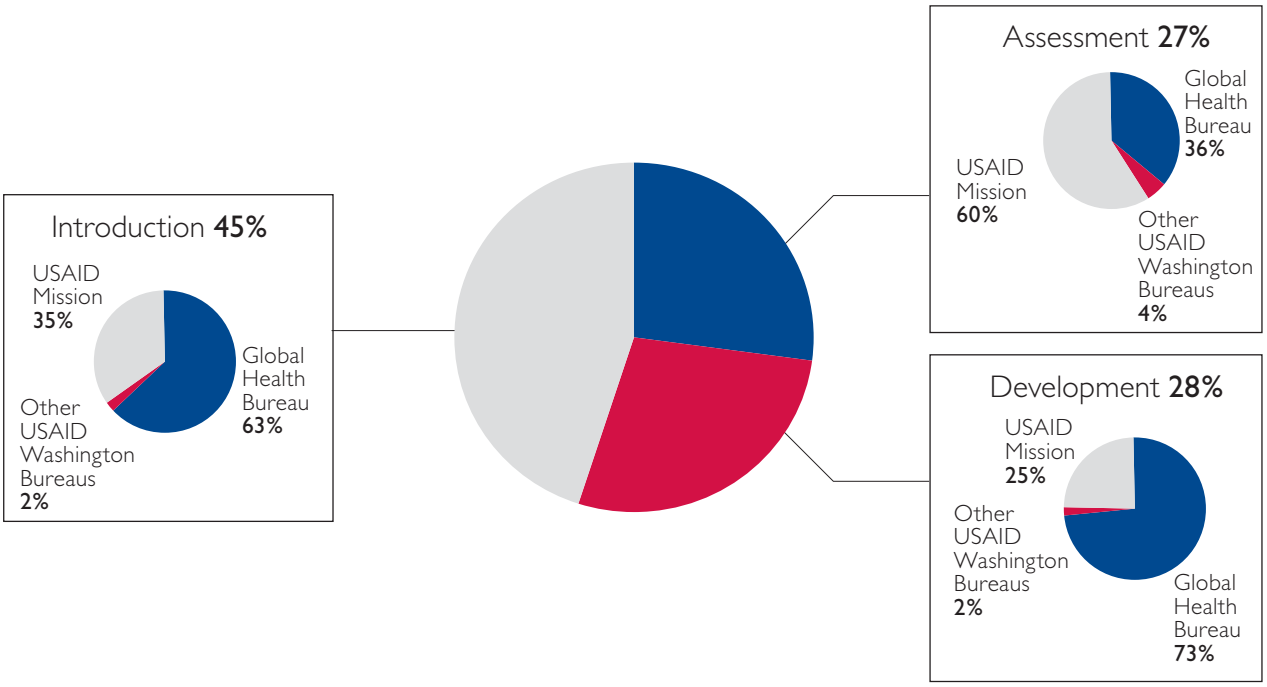


Table II.3 Research Activity by Recipient Type and Region of Activity, FY 2002-2004 (n=1321)

	Global	Africa	Asia and Near East	Europe & Eurasia	Latin America and the Caribbean	Total
Int'l Org	33	5	12	1	3	**54**
Host Gov.	4	4	10	1	6	**25**
University	53	46	62	5	6	**172**
NGO/PVO	0	4	34	4	11	**53**
HHS (NIH, CDC)	18	8	3	3	5	**37**
DOD	3	0	0	0	0	**3**
Collaborating Agencies and other partners	244	280	263	14	176	**977**
	355	**347**	**384**	**28**	**207**	**1321**

Figure II.9 Recipient of Funding for Research Activity, FY 2002-2004 (n=1321)

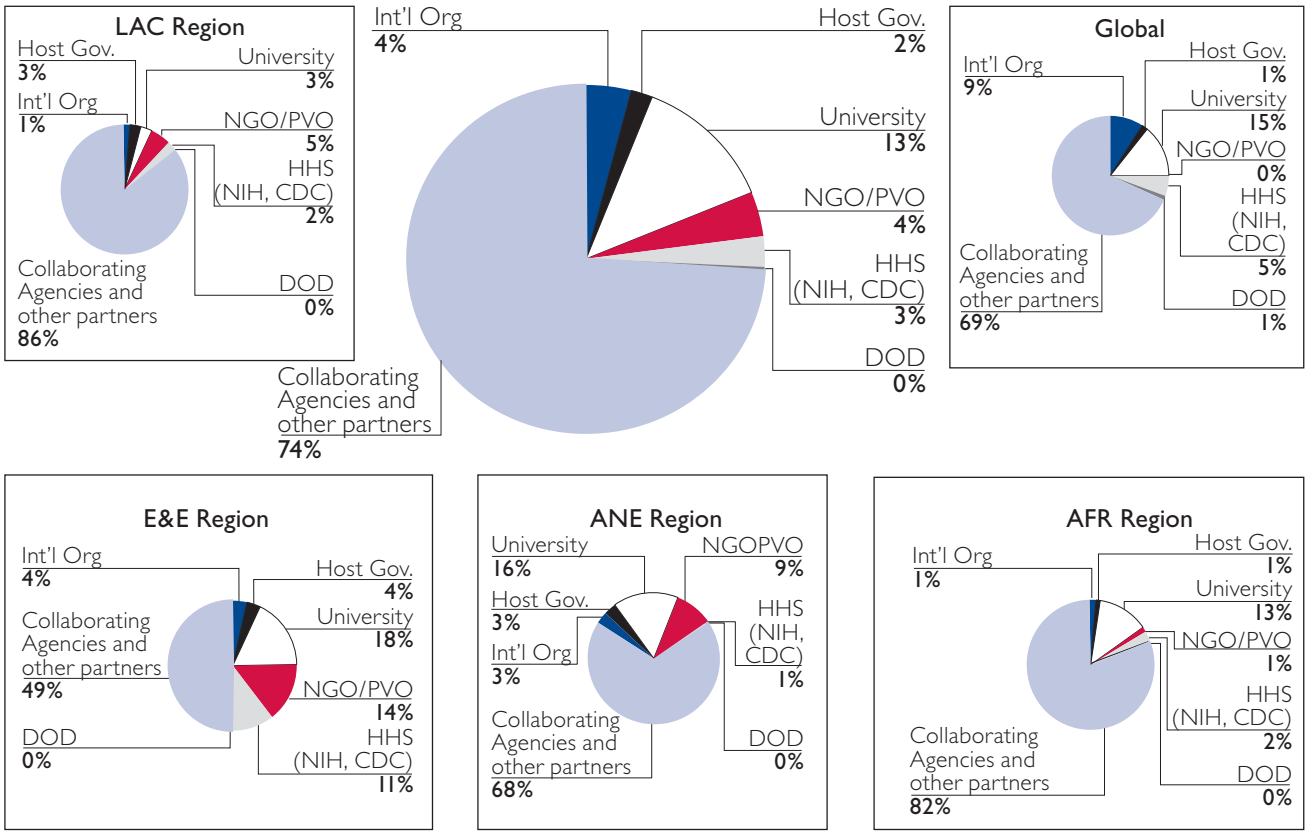
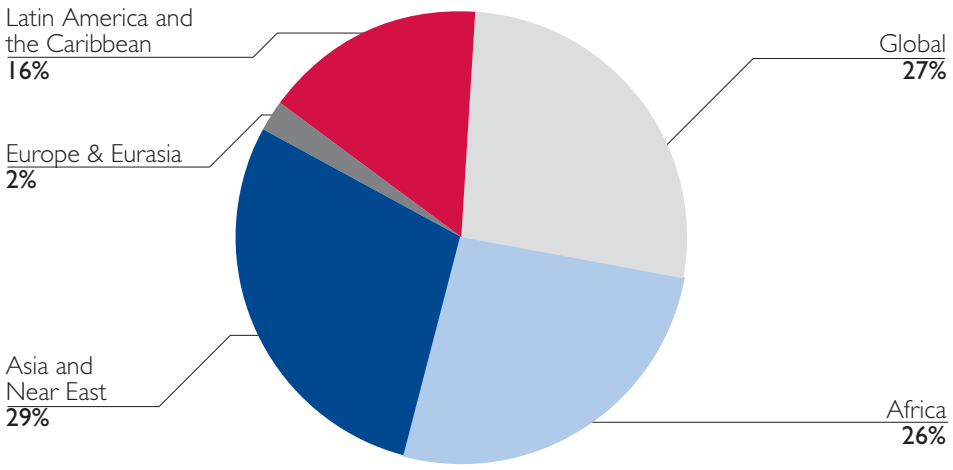


Figure II.10 Location of Research Activity, FY 2002-04 (n=1321)



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